

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: S. Kumar Examiner #: 64894 Date: 6/1/04
Art Unit: 1621 Phone Number: 202-272-0640 Serial Number: 10/606403
Mail Box and Bldg/Room Location: REM 5D6 Results Format Preferred (circle): PAPER DISK E-MAIL
5C18

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Novel process for preparing and isolating rac-bicalutamide

Inventors (please provide full names): Ben-Zion Dolitzky et al

Earliest Priority Filing Date: 6/13/2001

1. A process for the purification and isolation of bicalutamide by solution crystallization, comprising the steps of:

- (i) combining crude bicalutamide and a solvent;
5 (ii) crystallizing the bicalutamide from the solvent; and
(iii) collecting the crystals of bicalutamide.

2. The process of claim 1, wherein the the crystallizing step (ii) comprises seeding the bicalutamide suspension.

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3. The process of claim 1, further comprising heating the resulting bicalutamide solution to about the boiling point of the solvent.

4. The process of claim 1, wherein the solvent is selected from the group consisting
15 of water, methanol, ethanol, DCM, toluene, PE, chloroform, hexane, 1,2-dichloroethane, diethyl ether, propanol and isopropanol.

5. The process of claim 1, wherein the solvent is selected from the group consisting of ethanol, propanol and isopropanol.

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6. A process for the purification and isolation of bicalutamide by solution crystallization, comprising the steps of:

- (i) combining crude bicalutamide and a first solvent;
(ii) adding a second solvent to the crude bicalutamide-first solvent mixture;
25 (iii) crystallizing the bicalutamide from the solvents; and
(iv) collecting the crystals of bicalutamide.

7. The process of claim 6, further comprising heating the bicalutamide solution of step (i) to about the boiling point of the solvent.

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STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 123401

TO: Shailendra Kumar
Location: 5d61 / 5c18
Wednesday, June 02, 2004
Art Unit: 1621
Phone: 272-0640
Serial Number: 10 / 606403

From: Jan Delaval
Location: Biotech-Chem Library
Rem 1A51
Phone: 272-2504

jan.delaval@uspto.gov

Search Notes

=> fil reg

FILE 'REGISTRY' ENTERED AT 10:06:25 ON 02 JUN 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 1 JUN 2004 HIGHEST RN 688308-86-3
DICTIONARY FILE UPDATES: 1 JUN 2004 HIGHEST RN 688308-86-3

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

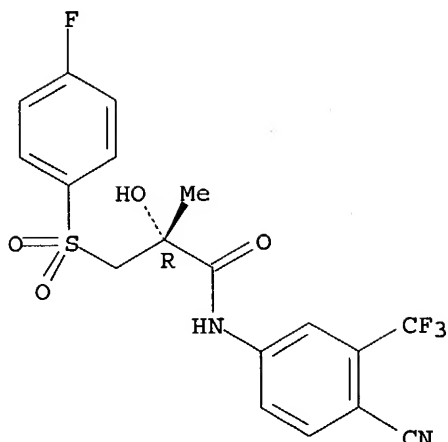
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

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L6 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 113299-40-4 REGISTRY
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (R)-
OTHER NAMES:
CN (R)-Bicalutamide
CN (R)-Casodex
FS STEREOSEARCH
MF C18 H14 F4 N2 O4 S
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, IMSPATENTS,
IMSRESEARCH, PS, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA Caplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC
(Process); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
study); FORM (Formation, nonpreparative); PREP (Preparation); PROC
(Process); USES (Uses)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

24 REFERENCES IN FILE CA (1907 TO DATE)
24 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:303414
REFERENCE 2: 139:375064
REFERENCE 3: 138:406952
REFERENCE 4: 138:343868
REFERENCE 5: 138:321017
REFERENCE 6: 138:24551
REFERENCE 7: 137:384623
REFERENCE 8: 137:284397
REFERENCE 9: 136:79780
REFERENCE 10: 135:313717

L6 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 113299-38-0 REGISTRY
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)-(9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (S)-

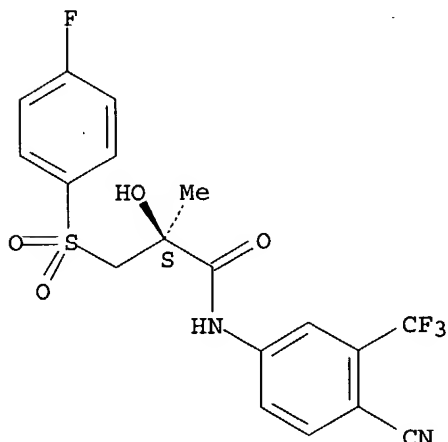
OTHER NAMES:

CN (S)-Casodex
FS STEREOSEARCH
MF C18 H14 F4 N2 O4 S
SR CA

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSPATENTS, IMSRESEARCH,
PS, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA Caplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC
(Process); USES (Uses)

RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation);
PROC (Process); USES (Uses)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13 REFERENCES IN FILE CA (1907 TO DATE)

13 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:24551
REFERENCE 2: 137:384623
REFERENCE 3: 136:79780
REFERENCE 4: 134:326279
REFERENCE 5: 134:86040
REFERENCE 6: 133:12739
REFERENCE 7: 130:49289
REFERENCE 8: 127:242768
REFERENCE 9: 124:306528
REFERENCE 10: 123:160082

L6 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN

RN 90357-06-5 REGISTRY

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (±)-

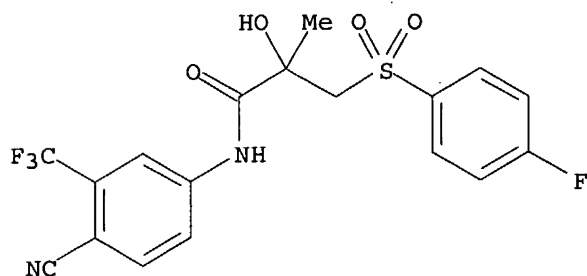
OTHER NAMES:

CN (±)-4'-Cyano-α,α,α-trifluoro-3-[(p-fluorophenyl)sulfonyl]-2-methyl-m-lactotoluidide

CN Bicalutamide

CN Casodex

CN Cosudex
CN ICI 176334
CN ZD 176334
DR 151262-58-7
MF C18 H14 F4 N2 O4 S
LC STN Files: ADISINSIGHT, ADISNEWS, BEILSTEIN*, BIOBUSINESS, BIOSIS,
BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN,
CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IMSCOSEARCH, IMSDRUGNEWS,
IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, PS,
RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO
DT.CA Caplus document type: Conference; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);
PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or
reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological
study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP
(Preparation); PROC (Process); PRP (Properties); USES (Uses)



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

358 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
359 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:368658
REFERENCE 2: 140:350595
REFERENCE 3: 140:332704
REFERENCE 4: 140:321363
REFERENCE 5: 140:315331
REFERENCE 6: 140:303414
REFERENCE 7: 140:292649
REFERENCE 8: 140:280889
REFERENCE 9: 140:270600
REFERENCE 10: 140:264968

=> d his

(FILE 'HOME' ENTERED AT 08:24:34 ON 02 JUN 2004)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 08:25:17 ON 02 JUN 2004

E BICALUTAMIDE/CN
L1 1 S E3
E BICALUTAMIDE
L2 3 S E3,L1
E C18H14F4N2O4S/MF
L3 4 S E3 NOT L2
L4 1 S L3 AND 2/NR
L5 4 S L1,L2,L4
L6 3 S L5 AND CASODEX
SEL RN
L7 0 S E1-E3/CRN

FILE 'HCAPLUS' ENTERED AT 08:28:32 ON 02 JUN 2004

L8 369 S L6
L9 459 S CASODEX OR BICALUTAMIDE OR COSUDEX OR ICI176334 OR ZD167334 O
L10 469 S L8,L9
L11 316 S L10 AND (PD<=20010613 OR PRD<=20010613 OR AD<=20010613)
L12 2 S (US20040044249 OR US6737550)/PN OR (WO2002-US18329 OR US2002-
E DOLITZKY B/AU
L13 28 S E4
E REANY OF/AU
L14 9 S E3,E4
E SHAMMAI J/AU
L15 2 S E4
E BIOGAL/PA,CS
L16 349 S E3-E43
E TEVA/PA,CS
L17 239 S E3-E75
E SHAMAI J/AU
L18 1 S E4
L19 2 S L10 AND L12-L18
E CRYSTAL/CT
L20 0 S E59-E61 AND L10
L21 0 S E64+OLD,NT,PFT AND L10
L22 0 S E103,E106 AND L10
L23 1 S E114+OLD,NT,PFT AND L10
L24 0 S E131+OLD,NT,PFT AND L10
L25 3 S E141+OLD,NT,PFT AND L10
L26 0 S E161+OLD,NT,PFT AND L10
L27 0 S E187 AND L10
L28 0 S E190+OLD,NT,PFT AND L10
L29 0 S E265+OLD,NT,PFT AND L10
L30 0 S E269+OLD,NT,PFT AND L10
L31 2 S E304+OLD,NT,PFT AND L10
L32 0 S E342+OLD,NT,PFT AND L10
L33 0 S E345+OLD,NT,PFT AND L10
L34 0 S E370+OLD,NT,PFT AND L10
E E304+ALL
L35 0 S L10 AND (E21+OLD,NT,PFT OR E22+OLD,NT,PFT OR E23+OLD,NT,PFT O
L36 0 S L10 AND E27+OLD,NT,PFT
L37 10 S L10 AND ?CRYS?
L38 1 S L10 AND CRYS?/SC,SX
L39 10 S L23,L25,L31,L37,L38
L40 4 S L39 AND L11
L41 3 S L6 (L) (PREP+NT OR PROC+NT)/RL AND L40
L42 1 S L41 AND PREPARATION/TI
L43 2 S L19,L42

L44 1 S ETHYL 2 4 FLUOROPHENYL SULFONE 2 HYDROXY PROPION?
L45 2 S L43,L44
SEL RN

FILE 'REGISTRY' ENTERED AT 08:58:29 ON 02 JUN 2004

L46 40 S E1-E40
L47 3 S L46 AND L6
L48 11 S 110-54-3 OR 108-88-3 OR 67-66-3 OR 67-63-0 OR 67-56-1 OR 64-1
L49 7 S 108-10-1 OR 67-68-5 OR 109-99-9 OR 141-78-6 OR 75-05-8 OR 67-
L50 1 S 109-72-8
L51 18 S L46 NOT L47-L50
L52 2 S L51 AND C8H5F3N2
L53 16 S L51 NOT L52
L54 1 S L53 AND C10H11FO3S
L55 1 S L53 AND C12H15FO5S
L56 14 S L53 NOT L54,L55

FILE 'HCAPLUS' ENTERED AT 09:04:57 ON 02 JUN 2004

L57 15 S L10 AND L48
L58 9 S L10 AND L49
L59 14 S L10 AND L52
L60 3 S L10 AND L50
L61 4 S L10 AND L54,L55
L62 20 S L11 AND L57-L61
L63 10 S L8 (L) PREP+NT/RL AND L62
L64 1 S L8 (L) PROC+NT/RL AND L62
L65 2 S L45 AND L62-L64
L66 8 S L63,L64 NOT L65
L67 11 S L6 (L) PREP+NT/RL AND L11
L68 29 S L6 (L) PROC+NT/RL AND L11
L69 1 S L67 NOT L65,L66
L70 28 S L68 NOT L66,L67
L71 10 S L65,L66 AND L8-L45,L57-L70

FILE 'WPIX' ENTERED AT 09:34:07 ON 02 JUN 2004

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E BICALUTAMIDE/DCN
E CASODEX/DCN
E R04776+ALL/DCN
E RA1M70+ALL/DCN
E BICALUTAMIDE/CN
L73 1 S E3
L74 1 S RA1M70/DCN
L75 123 S L72,L74
E BICALUTAM
L76 94 S E4-E6
E BICALUTAM/ABEX
L77 25 S E4
E CASODEX/BIX
E CASODEX/BI,ABEX
L78 31 S E3,E4
L79 124 S L75-L78
L80 12 S L79 AND ?CRYS?/BIX
SEL DN AN 4-7 11 12
L81 6 S L80 NOT E1-E12
L82 1 S L12
E BIOGAL/PA
L83 221 S E3-E11
E TEVA/PA
L84 238 S E3-E20
E DOLITZKY B/AU
L85 28 S E3,E4
E REANY O/AU

L86 2 S E3
 E SHAMMAI J/AU
 L87 2 S E3
 E SHAMMAI J/AU
 L88 1 S E3
 L89 1 S L79 AND L83-L88
 L90 7 S L82,L89,L81
 E RA37J7+ALL/DCN
 L91 9 S L79 AND C07C315/IC,ICM,ICS
 L92 10 S L90,L91 AND L72-L91

FILE 'REGISTRY' ENTERED AT 10:06:25 ON 02 JUN 2004

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 10:06:39 ON 02 JUN 2004

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FILE COVERS 1907 - 2 Jun 2004 VOL 140 ISS 23

FILE LAST UPDATED: 1 Jun 2004 (20040601/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L71 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 2004:182593 HCAPLUS
 DN 140:235504
 ED Entered STN: 05 Mar 2004
 TI Preparation and crystallization of
 bicalutamide
 IN Dolitzky, Ben-Zion; Reany, Ofer; Shammai,
 Jenny
 PA Israel
 SO U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No. 170,721.
 CODEN: USXXCO
 DT Patent
 LA English
 IC ICM C07C317-28
 NCL 564162000
 CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 63
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004044249	A1	20040304	US 2003-606403	20030625 <--
	US 2003045741	A1	20030306	US 2002-170721	20020613 <--
	US 6737550	B2	20040518		
	US 2004059147	A1	20040325	US 2003-668982	20030922 <--

PRAI US 2001-298009P P 20010613 <--
US 2002-371069P P 20020409 <--
US 2002-170721 A2 20020613

OS CASREACT 140:235504

AB Racemic N-[4-cyano-3-trifluoromethylphenyl]-3-[4-fluorophenylsulfonyl]-2-hydroxy-2-methylpropionamide (**bicalutamide**) was prepared starting from Et pyruvate and Me methacrylate. Thus, 5-amino-2-cyanobenzotrifluoride was treated with DABCO and reacted with deprotonated Et 2-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropionate (prepared from Et pyruvate) to give 40% **bicalutamide**. Micronized particles of **bicalutamide** can be obtained as pharmaceutical compns. that are useful for its anti-androgen activity (no data). **Bicalutamide** intermediates were also prepared, including Et 2-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropionate, Me 2,3-epoxy-2-methylpropionate and 2-hydroxy-2-methyl-3-(4-fluorophenylthio)propionic acid. The present invention further discloses the isolation and purification of **bicalutamide** by various **crystallization** methods.

ST **bicalutamide** prepn **crystn** micronization; cyanophenyl fluorophenylsulfonyl hydroxy propionamide prepn **crystn** micronization

IT Ligroine
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** solvent; preparation, micronization and **crystallization** of **bicalutamide**)

IT Drug delivery systems
(microparticles; preparation, micronization and **crystallization** of **bicalutamide**)

IT **Crystallization**
(preparation, micronization and **crystallization** of **bicalutamide**)

IT 60-29-7, Diethyl ether, uses 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 67-64-1, Acetone, uses 67-66-3, Chloroform, uses 67-68-5, DMSO, uses 68-12-2, DMF, uses 71-23-8, Propanol, uses 75-05-8, Acetonitrile, uses 75-09-2, Dichloromethane, uses 107-06-2, 1,2-Dichloroethane, uses 108-10-1, Isobutyl methyl ketone 108-88-3, Toluene, uses 109-99-9, THF, uses 110-54-3, Hexane, uses 141-78-6, Ethyl acetate, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** solvent; preparation, micronization and **crystallization** of **bicalutamide**)

IT 90357-06-5P, **Bicalutamide**
RL: PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); SPN (Synthetic preparation); PREP (Preparation); PROC (Process)
(preparation, micronization and **crystallization** of **bicalutamide**)

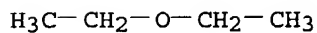
IT 80-62-6, Methyl methacrylate 371-42-6, 4-Fluorothiophenol 455-15-2, 4-Fluorophenyl methyl sulfone 617-35-6, Ethyl pyruvate 654-70-6, 4-Cyano-3-(trifluoromethyl)aniline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation, micronization and **crystallization** of **bicalutamide**)

IT 58653-97-7P, Methyl 2-methyl-2-oxiranecarboxylate 339530-91-5P 478190-74-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, micronization and **crystallization** of **bicalutamide**)

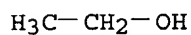
IT 60-29-7, Diethyl ether, uses 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 67-64-1, Acetone, uses 67-66-3, Chloroform, uses 67-68-5, DMSO, uses 68-12-2, DMF, uses 71-23-8, Propanol, uses 75-05-8, Acetonitrile, uses 75-09-2, Dichloromethane, uses 107-06-2, 1,2-Dichloroethane, uses

108-10-1, Isobutyl methyl ketone 108-88-3, Toluene, uses
 109-99-9, THF, uses 110-54-3, Hexane, uses
 141-78-6, Ethyl acetate, uses 7732-18-5, Water, uses
 RL: NUU (Other use, unclassified); USES (Uses)
 (crystallization solvent; preparation, micronization and crystallization
 of bicalutamide)

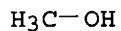
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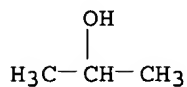
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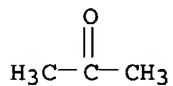
RN 67-56-1 HCAPLUS
 CN Methanol (8CI, 9CI) (CA INDEX NAME)



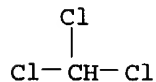
RN 67-63-0 HCAPLUS
 CN 2-Propanol (9CI) (CA INDEX NAME)



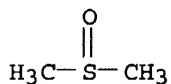
RN 67-64-1 HCAPLUS
 CN 2-Propanone (9CI) (CA INDEX NAME)



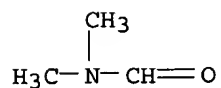
RN 67-66-3 HCAPLUS
 CN Methane, trichloro- (9CI) (CA INDEX NAME)



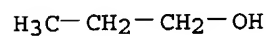
RN 67-68-5 HCAPLUS
 CN Methane, sulfinylbis- (9CI) (CA INDEX NAME)



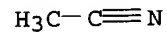
RN 68-12-2 HCAPLUS
CN Formamide, N,N-dimethyl- (8CI, 9CI) (CA INDEX NAME)



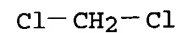
RN 71-23-8 HCAPLUS
CN 1-Propanol (9CI) (CA INDEX NAME)



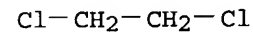
RN 75-05-8 HCAPLUS
CN Acetonitrile (8CI, 9CI) (CA INDEX NAME)



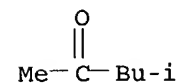
RN 75-09-2 HCAPLUS
CN Methane, dichloro- (8CI, 9CI) (CA INDEX NAME)



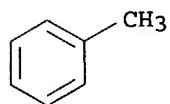
RN 107-06-2 HCAPLUS
CN Ethane, 1,2-dichloro- (8CI, 9CI) (CA INDEX NAME)



RN 108-10-1 HCAPLUS
CN 2-Pentanone, 4-methyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



RN 108-88-3 HCAPLUS
CN Benzene, methyl- (9CI) (CA INDEX NAME)



RN 109-99-9 HCAPLUS
CN Furan, tetrahydro- (7CI, 8CI, 9CI) (CA INDEX NAME)



RN 110-54-3 HCAPLUS
CN Hexane (8CI, 9CI) (CA INDEX NAME)

Me-(CH₂)₄-Me

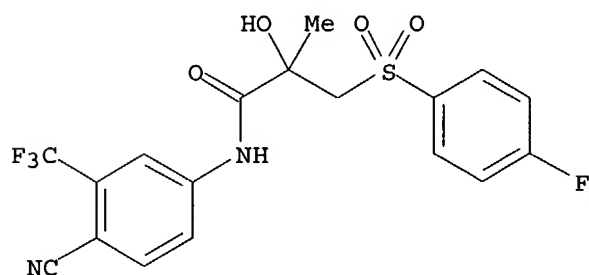
RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)

Et-O-Ac

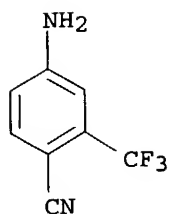
RN 7732-18-5 HCAPLUS
CN Water (8CI, 9CI) (CA INDEX NAME)

H₂O

IT 90357-06-5P, Bicalutamide
RL: PEP (Physical, engineering or chemical process); PUR
(Purification or recovery); PYP (Physical process);
SPN (Synthetic preparation); PREP (Preparation);
PROC (Process)
(preparation, micronization and crystallization of bicalutamide)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



IT 654-70-6, 4-Cyano-3-(trifluoromethyl)aniline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation, micronization and crystallization of bicalutamide)
RN 654-70-6 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



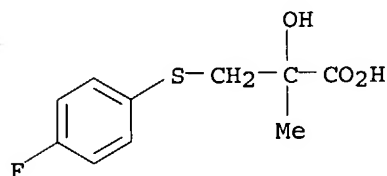
IT 339530-91-5P 478190-74-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation, micronization and crystallization of bicalutamide)

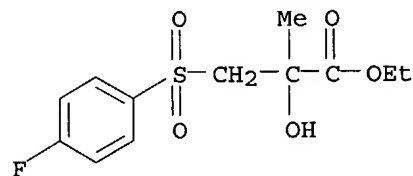
RN 339530-91-5 HCAPLUS

CN Propanoic acid, 3-[(4-fluorophenyl)thio]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 478190-74-8 HCAPLUS

CN Propanoic acid, 3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, ethyl ester (9CI) (CA INDEX NAME)



L71 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:964133 HCAPLUS

DN 138:24551

ED Entered STN: 20 Dec 2002

TI Preparation of rac-bicalutamide

IN Dolitzky, Ben-Zion; Reany, Ofer; Shamai, Jenny

PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.; Biogal Gyogyszergyar

SO PCT Int. Appl., 22 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K

CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

Section cross-reference(s): 1, 63

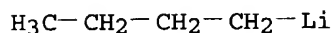
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002100339	A2	20021219	WO 2002-US18329	20020613 <--
	WO 2002100339	A3	20031016		

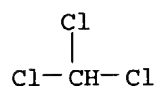
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 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
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 TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
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 EP 1406855 A2 20040414 EP 2002-739801 20020613 <--
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 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
 PRAI US 2001-298009P P 20010613 <--
 US 2002-371069P P 20020409 <--
 WO 2002-US18329 W 20020613 <--
 OS CASREACT 138:24551
 AB Racemic and optically active N-[4-cyano-3-trifluoromethylphenyl]-3-[4-
 fluorophenylsulfonyl]-2-hydroxy-2-Me propionamide (**bicalutamide**)
 were prepared starting from Et pyruvate and Me methacrylate. Thus,
 5-amino-2-cyanobenzotrifluoride was treated with DABCO and reacted with
 deprotonated **ethyl-[2-(4-fluorophenyl sulfone)]-2-hydroxy**
propionate (prepared from Et pyruvate) to give %40 rac-
bicalutamide. Micronized particles of rac-**bicalutamide**
 can be obtained as pharmaceutical compns. that are useful for its
 anti-androgen activity (no data). **Bicalutamide** intermediates
 were also prepared, including **ethyl-[2-(4-fluorophenyl sulfone)]-2-hydroxy**
propionate, 1,2-epoxy-2-Me propionate and 2-hydroxy-2-methyl-3-(4-
 fluorophenylthio) propionic acid.
 ST **bicalutamide** prepn; cyanotrifluoromethylphenylfluorophenylsulfonylhydroxymethylpropionamide prepn
 IT 280-57-9, DABCO
 RL: RGT (Reagent); RACT (Reactant or reagent)
 (anion stabilizer; preparation of rac-**bicalutamide**)
 IT 109-72-8, Butyl lithium, reactions 1310-58-3, Potassium
 hydroxide, reactions 1310-73-2, Sodium hydroxide, reactions
 RL: RGT (Reagent); RACT (Reactant or reagent)
 (base; preparation of rac-**bicalutamide**)
 IT 67-66-3, Chloroform, uses
 RL: NUU (Other use, unclassified); USES (Uses)
 (extraction with; preparation of rac-**bicalutamide**)
 IT 7727-37-9, Nitrogen, uses
 RL: NUU (Other use, unclassified); USES (Uses)
 (inert atmospheric; preparation of rac-**bicalutamide**)
 IT 478190-75-9 478190-76-0
 RL: FMU (Formation, unclassified); RCT (Reactant); FORM (Formation,
 nonpreparative); RACT (Reactant or reagent)
 (preparation of rac-**bicalutamide**)
 IT 141-78-6, Ethyl acetate, uses
 RL: NUU (Other use, unclassified); USES (Uses)
 (preparation of rac-**bicalutamide**)
 IT 80-62-6, Methyl methacrylate 371-42-6, 4-Fluorothiophenol 455-15-2,
 4-Fluorophenyl methyl sulfone 617-35-6, Ethyl pyruvate 654-70-6
 , 4-Cyano-3-(trifluoromethyl)aniline 37222-66-5, Oxone
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of rac-**bicalutamide**)
 IT 58653-97-7P, Methyl 2-methyl-2-oxiranecarboxylate 339530-91-5P
 478190-74-8P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (preparation of rac-**bicalutamide**)
 IT 7647-01-0, Hydrochloric acid, reactions 7664-38-2, Phosphoric acid,

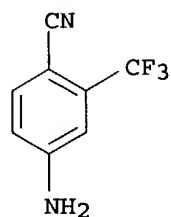
reactions 7697-37-2, Nitric acid, reactions
 RL: RGT (Reagent); RACT (Reactant or reagent)
 (preparation of rac-bicalutamide)
 IT 90357-06-5P, Bicalutamide 113299-38-0P
 113299-40-4P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of rac-bicalutamide)
 IT 60-29-7, Diethyl ether, uses 67-56-1, Methanol, uses
 109-99-9, THF, uses
 RL: NUU (Other use, unclassified); USES (Uses)
 (solvent; preparation of rac-bicalutamide)
 IT 109-72-8, Butyl lithium, reactions
 RL: RGT (Reagent); RACT (Reactant or reagent)
 (base; preparation of rac-bicalutamide)
 RN 109-72-8 HCAPLUS
 CN Lithium, butyl- (8CI, 9CI) (CA INDEX NAME)



IT 67-66-3, Chloroform, uses
 RL: NUU (Other use, unclassified); USES (Uses)
 (extraction with; preparation of rac-bicalutamide)
 RN 67-66-3 HCAPLUS
 CN Methane, trichloro- (9CI) (CA INDEX NAME)



IT 478190-76-0
 RL: FMU (Formation, unclassified); RCT (Reactant); FORM (Formation,
 nonpreparative); RACT (Reactant or reagent)
 (preparation of rac-bicalutamide)
 RN 478190-76-0 HCAPLUS
 CN Benzonitrile, 4-amino-2-(trifluoromethyl)-, monolithium salt (9CI) (CA
 INDEX NAME)

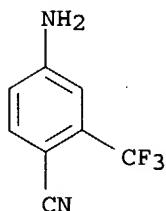


● Li

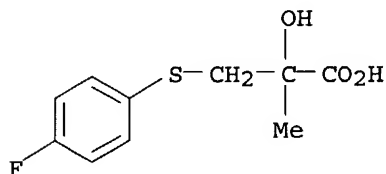
IT 141-78-6, Ethyl acetate, uses
 RL: NUU (Other use, unclassified); USES (Uses)
 (preparation of rac-bicalutamide)
 RN 141-78-6 HCAPLUS
 CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)

Et-O-Ac

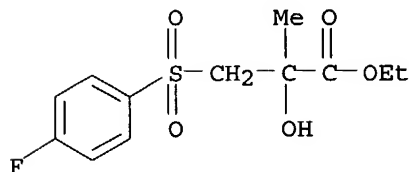
IT 654-70-6, 4-Cyano-3-(trifluoromethyl)aniline
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of rac-bicalutamide)
 RN 654-70-6 HCAPLUS
 CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



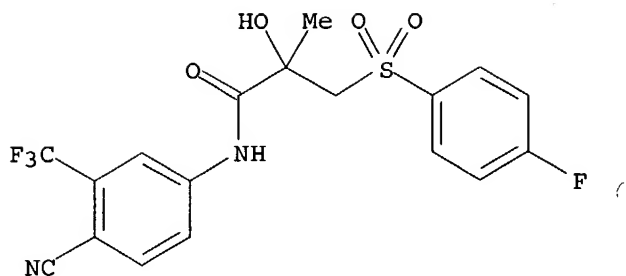
IT 339530-91-5P 478190-74-8P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (preparation of rac-bicalutamide)
 RN 339530-91-5 HCAPLUS
 CN Propanoic acid, 3-[(4-fluorophenyl)thio]-2-hydroxy-2-methyl- (9CI) (CA
 INDEX NAME)



RN 478190-74-8 HCAPLUS
 CN Propanoic acid, 3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, ethyl
 ester (9CI) (CA INDEX NAME)



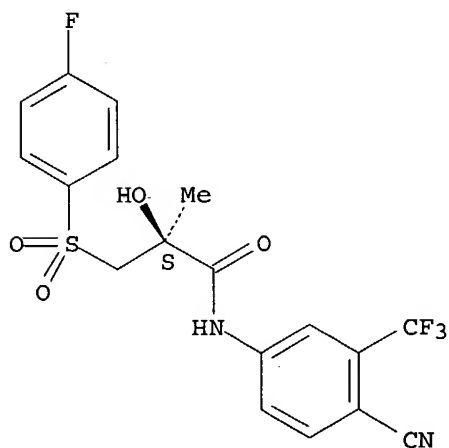
IT 90357-06-5P, Bicalutamide 113299-38-0P
 113299-40-4P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of rac-bicalutamide)
 RN 90357-06-5 HCAPLUS
 CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
 fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 113299-38-0 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

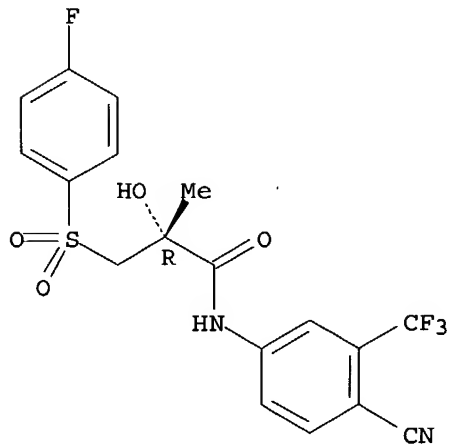
Absolute stereochemistry. Rotation (+).



RN 113299-40-4 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

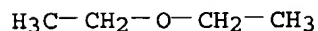


IT 60-29-7, Diethyl ether, uses 67-56-1, Methanol, uses 109-99-9, THF, uses

RL: NUU (Other use, unclassified); USES (Uses)
(solvent; preparation of rac-bicalutamide)

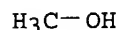
RN 60-29-7 HCAPLUS

CN Ethane, 1,1'-oxybis- (9CI) (CA INDEX NAME)



RN 67-56-1 HCAPLUS

CN Methanol (8CI, 9CI) (CA INDEX NAME)



RN 109-99-9 HCAPLUS

CN Furan, tetrahydro- (7CI, 8CI, 9CI) (CA INDEX NAME)



L71 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:850359 HCAPLUS

DN 137:337686

ED Entered STN: 08 Nov 2002

TI Preparation of acylanilide derivatives and bicalutamide via
amidation and alkylation

IN Ekwuribe, Nnochiri N.; James, Kenneth D.

PA USA

SO U.S. Pat. Appl. Publ., 12 pp.

CODEN: USXXCO

DT Patent

LA English

IC ICM C07C255-49

ICS C07C235-32

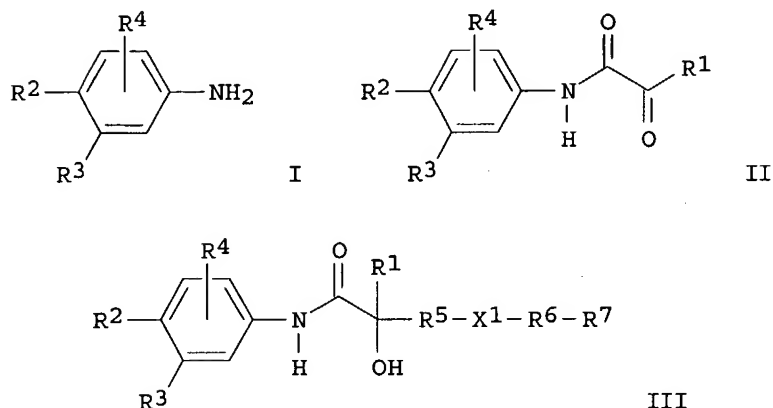
NCL 558418000

CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	US 2002165406	A1	20021107	US 2001-847229	20010502 <--
	US 6479692	B1	20021112		
	WO 2002088070	A1	20021107	WO 2002-US13591	20020502 <--
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	LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,				
	PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,				
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	TJ, TM				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,				
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	BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP	1383735	A1	20040128	EP 2002-734091	20020502 <--
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	US 2003045742	A1	20030306	US 2002-268155	20021010 <--
PRAI	US 2001-847229	A	20010502	<--	

WO 2002-US13591 W 20020502
 OS CASREACT 137:337686; MARPAT 137:337686
 GI



AB The method of preparation for acylanilides, including **bicalutamide**, is outlined under various conditions using carboxylic acid halogenating compds. in the amidation step and organometallic agents in the alkylation step. The acylanilides were prepared by reacting oxocarboxylic acids R_1CO_2H (R_1 = alkyl, haloalkyl) with anilines I (R_2 = cyano, NO_2 , Ph, etc., R_3 = F, alkylsulfinyl, PhS, etc., R_4 = H, halogen), which gave the corresponding amides II. The intermediate amides were then alkylated with $R_5-X_1-R_6-R_7$ (R_5 = unsubstituted or substituted alkyl up to 6 carbons, R_6 = direct link or unsubstituted or substituted alkyl up to 6 carbons, R_7 = alkyl, alkenyl, cycloalkyl, etc., X_1 = O, S, SO_2 , etc.) to give the final acylanilide derivs. III. **Bicalutamide** was synthesized using this method by treating pyruvic acid with $COCl_2$ and 4-cyano-3-(trifluoromethyl)aniline to give N-[4-cyano-3-(trifluoromethyl)phenyl]-2-oxopropionamide, which was then alkylated with 4-trifluorophenyl Me sulfone after treatment with BuLi.

ST **bicalutamide** prepn; acylanilide prepn; alkylation acylanilide prepn; amidation acylanilide prepn; anilide acyl prepn

IT Anilides

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(acyl; preparation of acylanilides and **bicalutamide** via amidation and alkylation)

IT Alkylation

Amidation

(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

IT 87310-69-8P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of acylanilides and **bicalutamide** via amidation and alkylation)

IT 90357-06-5P, **Bicalutamide**

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

IT 127-17-3, Pyruvic acid, reactions 455-15-2 654-70-6,
 4-Cyano-3-(trifluoromethyl)aniline

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

IT 109-72-8, Butyllithium, reactions 507-16-4, Thionyl bromide
7719-09-7, Thionyl chloride

RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

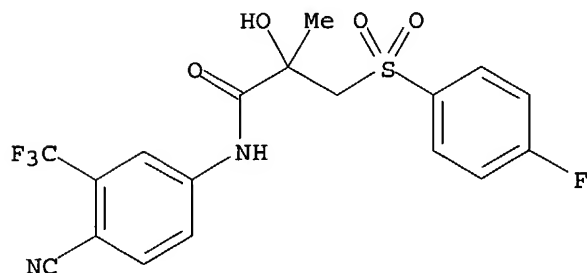
IT 90357-06-5P, Bicalutamide

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)

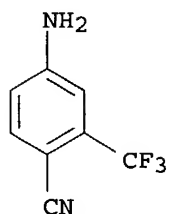


IT 654-70-6, 4-Cyano-3-(trifluoromethyl)aniline

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

RN 654-70-6 HCAPLUS

CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)

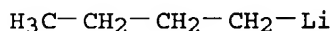


IT 109-72-8, Butyllithium, reactions

RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

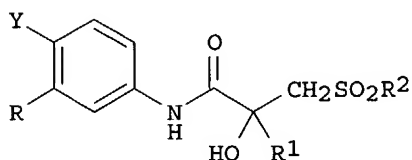
RN 109-72-8 HCAPLUS

CN Lithium, butyl- (8CI, 9CI) (CA INDEX NAME)

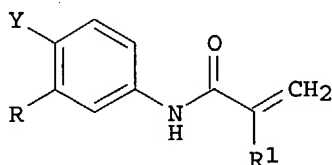


ED Entered STN: 28 Mar 2002
 TI Process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compounds
 IN Chen, Bang-Chi; Sundeen, Joseph E.; Zhao, Rulin
 PA Bristol-Myers Squibb Company, USA
 SO PCT Int. Appl., 26 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM C07C317-46
 ICS C07C315-02; C07C323-62; C07C319-14; C07D303-48; C07D301-16; C07C255-66; C07C253-30; C07C231-08
 CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 45
 FAN.CNT 1

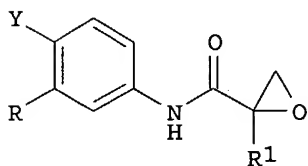
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002024638	A1	20020328	WO 2001-US42171	20010917 <--
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	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
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	US 6562994	B2	20030513		
	EP 1322603	A1	20030702	EP 2001-975752	20010917 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
	JP 2004509164	T2	20040325	JP 2002-529051	20010917 <--
PRAI	US 2000-234121P	P	20000921 <--		
	WO 2001-US42171	W	20010917		
OS	CASREACT 136:262992; MARPAT 136:262992				
GI					



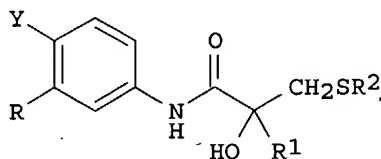
I



II



III



IV

AB The title compds. [I; Y = cyano, nitro, perfluoroalkyl, alkylcarbonyl,

alkoxycarbonyl, alkylsulfonyl; R = perfluoroalkyl, cyano, nitro, alkylcarbonyl, alkoxycarbonyl, alkyl, alkoxy; R1 = (halo)alkyl; R2 = alkyl, aryl, heteroaryl; e.g., **bicalutamide**, useful for the treatment of androgen-mediated diseases (no data), are prepared without the use of chromatog. sepns. and expensive starting materials by phenylating propenamides $H_2NCO(R_1):CH_2$ (e.g., methacrylamide) with leaving group-substituted benzenes 1,2,4-C₆H₃Y(R)X (X = F, Cl, Br, I, SO₃R₃; R₃ = alkyl, aryl; e.g., 4-fluoro-2-trifluoromethylbenzonitrile) so as to form a N-phenyl-substituted propenamides [II; e.g., N-[4-Cyano-3-(trifluoromethyl)phenyl]methacrylamide] which are then oxidized into the corresponding epoxides [III; e.g., N-[4-Cyano-3-(trifluoromethyl)phenyl]methacrylamide epoxide], converted into thioethers [IV; e.g., N-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)thio]-2-hydroxy-2-methylpropanamide] by reaction with mercaptans R₂SH (e.g., 4-fluorothiophenol), and then oxidized into their corresponding sulfones.

ST **bicalutamide** prepn

IT Aryl halides

RL: RCT (Reactant); RACT (Reactant or reagent)
(N-arylation of propenamides with)

IT Metal alkoxides

RL: RGT (Reagent); RACT (Reactant or reagent)
(alkali metal, bases; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Alkali metal compounds

RL: RGT (Reagent); RACT (Reactant or reagent)
(alkoxides, bases; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Alkali metal hydrides

RL: RGT (Reagent); RACT (Reactant or reagent)
(bases; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Thiols (organic), reactions

RL: RCT (Reactant); RACT (Reactant or reagent)
(formation of hydroxy-substituted thioethers from the reaction of epoxides with)

IT Aromatic hydrocarbons, uses

Hydrocarbons, uses

RL: NUU (Other use, unclassified); USES (Uses)
(halo, solvents; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Amides, preparation

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(hydroxy; process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Epoxidation

(of N-phenylpropenamides)

IT Epoxides

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(of N-phenylpropenamides in the preparation of intermediates in the preparation of antiandrogenic compds.)

IT Phenylation

(of propenamides in the preparation of intermediates in the preparation of antiandrogenic compds.)

IT Oxidation

(of thioethers into sulfones in the preparation of antiandrogenic compds.)

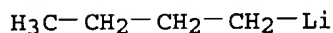
- IT Carboxylic acids, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(peroxy, oxidants; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
- IT Amides, uses
Aromatic hydrocarbons, uses
Esters, uses
Ethers, uses
Hydrocarbons, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvents; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
- IT 109-72-8, Butyl lithium, reactions 865-47-4 7646-69-7, Sodium hydride 7782-92-5, Sodium amide
RL: RGT (Reagent); RACT (Reactant or reagent)
(base; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
- IT 79-39-0, Methacrylamide 371-42-6, 4-Fluorothiophenol 407-25-0, Trifluoroacetic anhydride 7722-84-1, Hydrogen peroxide, reactions 194853-86-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
- IT 90356-78-8P 90357-51-0P 90357-53-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
- IT 359-48-8P, Trifluoroperacetic acid
RL: PNU (Preparation, unclassified); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(oxidant; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
- IT 79-21-0, Peracetic acid 937-14-4, 3-Chloroperbenzoic acid 7529-22-8, N-Methylmorpholine N-oxide 7790-28-5, Sodium periodate 37222-66-5, Oxone
RL: RCT (Reactant); RACT (Reactant or reagent)
(oxidant; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
- IT 90357-06-5P, Bicalutamide
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
- IT 68-12-2, Dmf, uses 75-09-2, Dichloromethane, uses 109-99-9, Thf, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

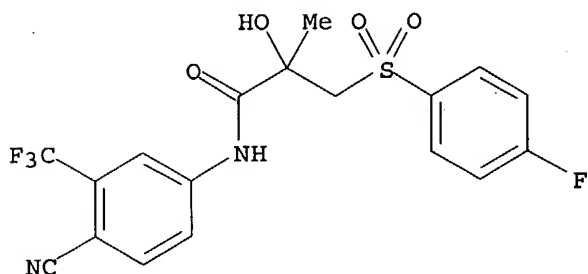
RE

- (1) Emmons, W; J AM CHEM SOC 1955, V77(1), P89
- (2) Itoh, H; US 4835312 A 1989 HCAPLUS
- (3) Tucker, H; US 4636505 A 1987 HCAPLUS
- (4) Venier, C; J ORG CHEM 1982, V47(19), P3773 HCAPLUS

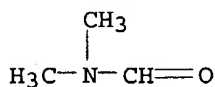
IT 109-72-8, Butyl lithium, reactions
 RL: RGT (Reagent); RACT (Reactant or reagent)
 (base; in a process for the preparation of N-(substituted phenyl)-3-alkyl-,
 aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and
 haloalkylpropanamide antiandrogenic compds.)
 RN 109-72-8 HCAPLUS
 CN Lithium, butyl- (8CI, 9CI) (CA INDEX NAME)



IT 90357-06-5P, Bicalutamide
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and
 heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide
 antiandrogenic compds.)
 RN 90357-06-5 HCAPLUS
 CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
 fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



IT 68-12-2, Dmf, uses 75-09-2, Dichloromethane, uses
 109-99-9, Thf, uses
 RL: NUU (Other use, unclassified); USES (Uses)
 (solvent; in a process for the preparation of N-(substituted
 phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and
 haloalkylpropanamide antiandrogenic compds.)
 RN 68-12-2 HCAPLUS
 CN Formamide, N,N-dimethyl- (8CI, 9CI) (CA INDEX NAME)



RN 75-09-2 HCAPLUS
 CN Methane, dichloro- (8CI, 9CI) (CA INDEX NAME)



RN 109-99-9 HCAPLUS
 CN Furan, tetrahydro- (7CI, 8CI, 9CI) (CA INDEX NAME)



L71 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 2001:359958 HCAPLUS
 DN 134:366692
 ED Entered STN: 18 May 2001
 TI Resolution of intermediates in the synthesis of enantiomeric
bicalutamide and analogs
 IN Ekwuribe, Nnochiri N.; James, Kenneth D.
 PA Nobex Corporation, USA
 SO PCT Int. Appl., 27 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM C07C315-06
 ICS C07C317-28
 CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2001034563	A1	20010517	WO 2000-US41609	20001025 <--	
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	RW:			GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		
	BR 2000015124	A	20020702	BR 2000-15124	20001025 <--	
	EP 1224167	A1	20020724	EP 2000-989719	20001025 <--	
	R:			AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL		
	JP 2003513955	T2	20030415	JP 2001-536512	20001025 <--	
	US 6593492	B1	20030715	US 2000-695884	20001025 <--	
	NZ 518552	A	20031031	NZ 2000-518552	20001025 <--	
	ZA 2002003228	A	20030723	ZA 2002-3228	20020423 <--	
	NO 2002001999	A	20020620	NO 2002-1999	20020426 <--	
PRAI	US 1999-161884P	P	19991027 <--			
	WO 2000-US41609	W	20001025 <--			
OS	MARPAT 134:366692					
AB	Title enantiomeric acylanilides were prepared by resolution of R4ZZ1Z2CR1(OH)CO2H [R1 = (halo)alkyl; R4 = (hydroxy)alkyl, alkenyl, (un)substituted Ph, etc.; Z = bond or alkylene; Z1 = O, SO0-2, (alkyl)imino; Z2 = alkylene] followed by amidation.					
ST	enantiomeric bicalutamide analog intermediate resolu					
IT	339530-92-6P					
	RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (resolution of intermediates in the synthesis of enantiomeric bicalutamide and analogs)					
IT	90357-06-5P, Bicalutamide					
	RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation) (resolution of intermediates in the synthesis of enantiomeric bicalutamide and analogs)					
IT	339530-91-5					

RL: RCT (Reactant); RACT (Reactant or reagent)
(resolution of intermediates in the synthesis of enantiomeric
bicalutamide and analogs)

IT 339530-94-8P

RL: SPN (Synthetic preparation); PREP (Preparation)
(resolution of intermediates in the synthesis of enantiomeric
bicalutamide and analogs)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Pfizer; WO 9408986 A 1994 HCAPLUS

(2) Sepracor Inc; WO 9519770 A 1995 HCAPLUS

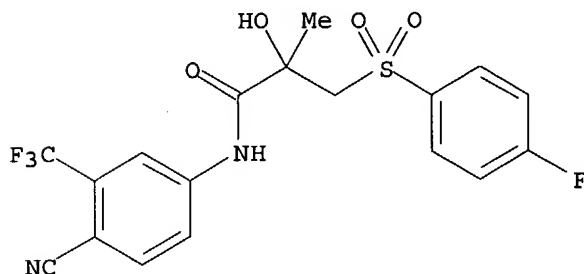
(3) Tucker, H; JOURNAL OF MEDICINAL CHEMISTRY 1988, V31(4), P885 HCAPLUS

IT 90357-06-5P, Bicalutamide

RL: IMF (Industrial manufacture); SPN (Synthetic
preparation); PREP (Preparation)
(resolution of intermediates in the synthesis of enantiomeric
bicalutamide and analogs)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)

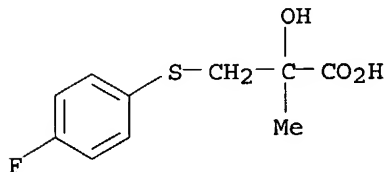


IT 339530-91-5

RL: RCT (Reactant); RACT (Reactant or reagent)
(resolution of intermediates in the synthesis of enantiomeric
bicalutamide and analogs)

RN 339530-91-5 HCAPLUS

CN Propanoic acid, 3-[(4-fluorophenyl)thio]-2-hydroxy-2-methyl- (9CI) (CA
INDEX NAME)



L71 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:300671 HCAPLUS

DN 134:326279

ED Entered STN: 27 Apr 2001

TI Asymmetric synthesis and antiandrogenic use of enantiomers of
Casodex (bicalutamide) and derivatives from enantiomers
of citramalic acid or proline.

IN Ekwuribe, Nnochiri

PA Nobex Corporation, USA

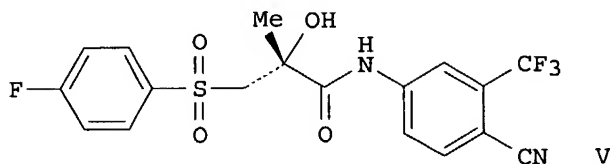
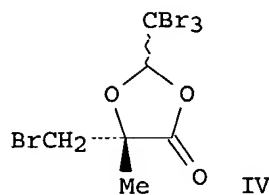
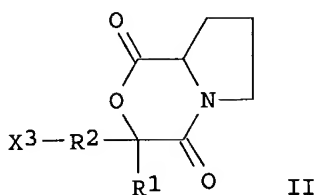
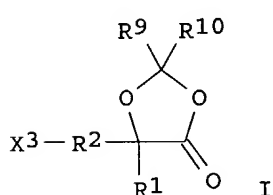
SO PCT Int. Appl., 44 pp.

CODEN: PIXXD2

DT Patent
 LA English
 IC ICM C07C315-00
 CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 2, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001028990	A2	20010426	WO 2000-US41233	20001018 <--
	WO 2001028990	A3	20010907		
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	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	EP 1222165	A2	20020717	EP 2000-982690	20001018 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
	BR 2000014889	A	20021231	BR 2000-14889	20001018 <--
	JP 2003512351	T2	20030402	JP 2001-531790	20001018 <--
	US 6583306	B1	20030624	US 2000-691621	20001018 <--
	NZ 518392	A	20040227	NZ 2000-518392	20001018 <--
	ZA 2002002947	A	20030715	ZA 2002-2947	20020415 <--
	NO 2002001831	A	20020619	NO 2002-1831	20020418 <--
	US 2004030130	A1	20040212	US 2003-444343	20030523 <--
PRAI	US 1999-160412P	P	19991019		<--
	US 2000-691621	A3	20001018		<--
	WO 2000-US41233	W	20001018		<--
OS	CASREACT 134:326279; MARPAT 134:326279				
GI					



AB A method of synthesizing pure enantiomers of acylanilides such as **Casodex (bicalutamide)** is disclosed. The method involves contacting certain ring compds. including I, II, or similar gem-disubstituted epoxides with nucleophiles R7-R6-X1H under conditions

sufficient to provide a compound R7-R6-X2-R2-C(OH)(R1)-CO2H [wherein; R1 is alkyl or haloalkyl up to C4; R2 is alkyl up to C6; R6 is a bond or alkyl up to C6; R7 is alk(en)yl, hydroxyalkyl, etc. or R7 is Ph (substituted with up to 3 substituents chosen from H, halo, nitro, carboxy, carbamoyl, etc.); X1 is O, SOO-2, or (alkyl)imino; X2 is O, S(O)O-2 or (oxidized)(alkyl)imino; X3 is a leaving group]. The starting ring compds. are those that, when opened, provide a substituent -R2-C(OH)(R1)-R3 [wherein; R3 is CH2OR4, where R4 is H, PhCH2, C(O)CH3, C(O)OR5, where R5 is H or alkyl]. In an exemplary embodiment, readily available (S)-citramalic acid is reacted with bromal to yield I (R9 = H, R10 is CBr3, R1 is β -Me, R2 is α -CH2 and X3 is CO2H; III). Compound III is condensed with 2-mercaptopyridine-N-oxide using DCC in CBrCl3 (solvent) at reflux which resulted in α -bromination/decarboxylation to IV. Intermediate IV was sequentially treated with base and 4-fluorobenzenethiol, coupled with 4-amino-2-trifluoromethylbenzonitrile and oxidized with mCPBA to give (R)-**Casodex** (V). The order of steps in the conversion of I or II to compds. exemplified by V may vary (e.g. substitution and oxidation of a sidechain of I may precede ring opening). The conversion of (R)-citramalic acid to (S)-**Casodex** is also claimed. Addnl., the invention mentions a modification of a route previously described for the transformation of (R)- and (S)-proline to (R)- and (S)-**Casodex** that improves yield proceeding through a proline-derived intermediate II. Biol. data comparing (R)-, (S)- and (+)-**Casodex**, synthesized by this method, in lowering testosterone response showed (R)-**Casodex** to be substantially more potent than the (S)-isomer.

- ST citramalic acid **Casodex bicalutamide** prepn amide
nitrile sulfone; prostate cancer **Casodex bicalutamide**
amide nitrile sulfone epoxide; asym synthesis **Casodex**
bicalutamide nitrile sulfone epoxide; proline **Casodex**
conversion improved
- IT Androgens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antiandrogens; asym. synthesis (and use) of (R)- and (S)-**Casodex (bicalutamide)** from (S)- and (R)-citramalic acid)
- IT Antitumor agents
Asymmetric synthesis and induction
(asym. synthesis (and use) of (R)- and (S)-**Casodex (bicalutamide)** from (S)- and (R)-citramalic acid)
- IT Prostate gland
(neoplasm, treatment of with enantiomeric **Casodex**; asym. synthesis (and use) of (R)- and (S)-**Casodex (bicalutamide)** from (S)- and (R)-citramalic acid)
- IT 90357-06-5, **Casodex**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(asym. synthesis (and use) of (R)- and (S)-**Casodex (bicalutamide)** from (S)- and (R)-citramalic acid)
- IT 113299-38-0P, S-**Casodex** 113299-40-4P, R-**Casodex**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(asym. synthesis (and use) of (R)- and (S)-**Casodex (bicalutamide)** from (S)- and (R)-citramalic acid)
- IT 90357-17-8P 335595-47-6P 335595-50-1P 335595-52-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

IT 115-17-3, Bromal 371-42-6, 4-Fluorobenzenethiol 597-44-4, Citramalic acid 654-70-6, 4-Amino-2-trifluoromethylbenzonitrile 1121-31-9, 2-Mercaptopyridine N-oxide 6236-09-5, S-Citramalic acid 6236-10-8, R-Citramalic acid

RL: RCT (Reactant); RACT (Reactant or reagent)

(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

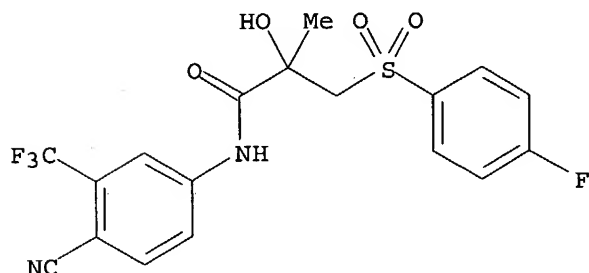
IT 90357-06-5, **Casodex**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



IT 113299-38-0P, S-**Casodex** 113299-40-4P, R-**Casodex**

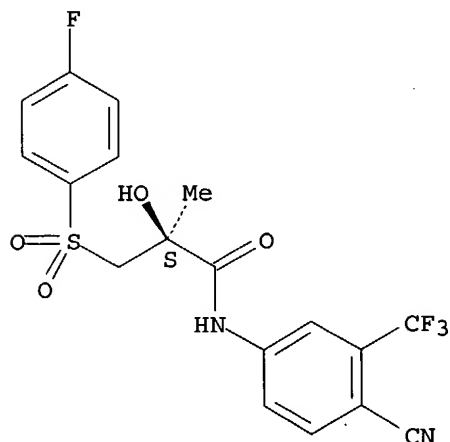
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

RN 113299-38-0 HCAPLUS

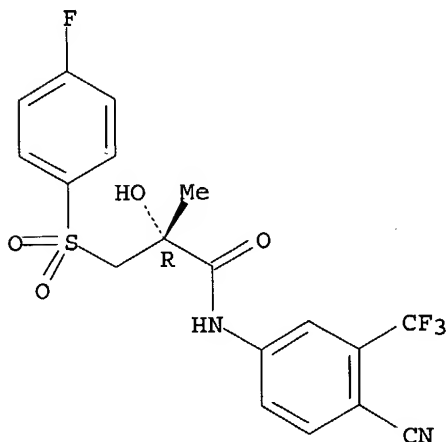
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

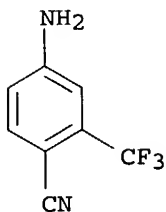


RN 113299-40-4 HCAPLUS
 CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 654-70-6, 4-Amino-2-trifluoromethylbenzonitrile
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (asym. synthesis (and use) of (R)- and (S)-Casodex (bicalutamide) from (S)- and (R)-citramalic acid)
 RN 654-70-6 HCAPLUS
 CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



L71 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 2001:12441 HCAPLUS
 DN 134:86040
 ED Entered STN: 05 Jan 2001
 TI Preparation of **bicalutamide** enantiomers
 IN Soros, Bela; Tuba, Zoltan; Galik, Gyorgy; Bor, Adam; Demeter, Adam; Trischler, Ferenc; Horvath, Janos; Brlik, Janos
 PA Richter Gedeon Vegyeszeti Gyar Rt., Hung.
 SO PCT Int. Appl., 33 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM C07D327-10
 ICS C07C253-30; C07C303-28; C07C309-66; C07C319-14; C07C323-60; C07C315-02; C07C317-46
 CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000608	A1	20010104	WO 2000-HU49	20000526 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1189898 A1 20020327 EP 2000-937111 20000526 <--
 EP 1189898 B1 20030312
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
 AT 234294 E 20030315 AT 2000-937111 20000526 <--
 ES 2188550 T3 20030701 ES 2000-937111 20000526 <--
 PRAI HU 1999-1937 A 19990610 <--
 WO 2000-HU49 W 20000526 <--

OS CASREACT 134:86040
 AB Racemic HOCH₂CMe(OH)CO₂H was optically resolved and the enantiomers treated with SOCl₂ to give the dioxthiolanonecarbonyl chloride which was amidated by H₂NC₆H₃(CF₃)(CN)-3,4. The deprotected dihydroxyamide was O-acylated by RSO₂Cl (R = 4-Me- or -BrC₆H₄) and the product thioetherified by 4-FC₆H₄SNa to give, after oxidation, the title compds.

ST **bicalutamide** enantiomer prepn
 IT 316373-87-2P 316373-88-3P
 RL: IMF (Industrial manufacture); PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of **bicalutamide** enantiomers)

IT 90356-78-8P 90357-17-8P 90357-18-9P 149404-64-8P 316373-86-1P
 316373-89-4P 316373-90-7P 316373-91-8P 316373-92-9P 316373-93-0P
 316373-94-1P 316373-95-2P 316373-96-3P 316373-97-4P 316373-98-5P
 316373-99-6P 316374-00-2P 316374-01-3P 316374-02-4P 316374-03-5P
 RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of **bicalutamide** enantiomers)

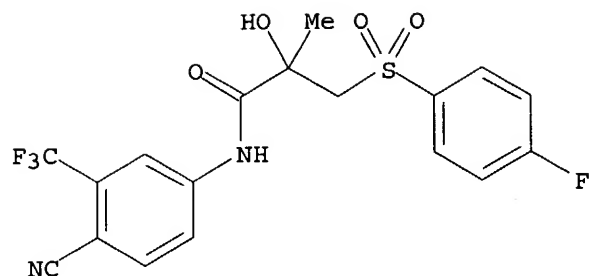
IT 90357-06-5P 113299-38-0P 113299-40-4P
 RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
 (preparation of **bicalutamide** enantiomers)

IT 98-58-8, p-Bromobenzenesulfonyl chloride 98-59-9, p-Toluenesulfonyl chloride 371-42-6, 4-Fluorothiophenol 654-70-6, 4-Cyano-3-trifluoromethylaniline 21620-60-0, 2,3-Dihydroxy-2-methylpropionic acid 99306-87-3
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of **bicalutamide** enantiomers)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
 RE
 (1) Imperial Chemical Industries; EP 0100172 A 1984 HCAPLUS
 (2) Tucker, H; JOURNAL OF MEDICINAL CHEMISTRY 1988, V31(4), P885 HCAPLUS
 (3) Tucker, H; JOURNAL OF MEDICINAL CHEMISTRY 1988, V31(5), P954 HCAPLUS

IT 90357-06-5P 113299-38-0P 113299-40-4P
 RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
 (preparation of **bicalutamide** enantiomers)

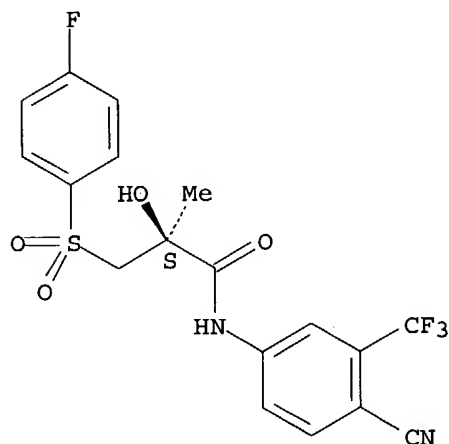
RN 90357-06-5 HCAPLUS
 CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 113299-38-0 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

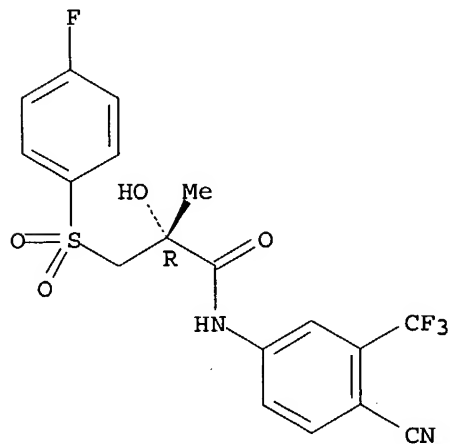
Absolute stereochemistry. Rotation (+).



RN 113299-40-4 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



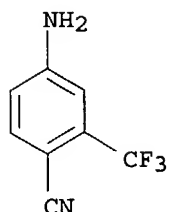
IT 654-70-6, 4-Cyano-3-trifluoromethylaniline

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of bicalutamide enantiomers)

RN 654-70-6 HCAPLUS

CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



L71 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1988:161557 HCAPLUS

DN 108:161557

ED Entered STN: 13 May 1988

TI Nonsteroidal antiandrogens. Synthesis and structure-activity relationships of 3-substituted derivatives of 2-hydroxypropionanilides

AU Tucker, Howard; Crook, J. W.; Chesterson, G. J.

CS Pharm. Div., Imp. Chem. Ind. PLC, Macclesfield/Cheshire, AK10 4TG, UK

SO Journal of Medicinal Chemistry (1988), 31(5), 954-9

CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

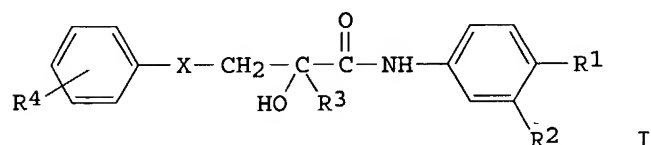
LA English

CC 2-2 (Mammalian Hormones)

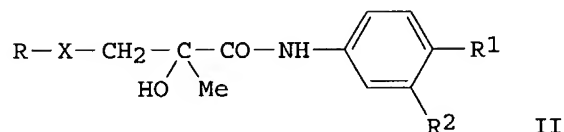
Section cross-reference(s): 1

OS CASREACT 108:161557

GI



I



II

AB A series of hydroxypropionanilides of general structure I and II ($R_1, R_2 = \text{NO}_2, \text{CF}_3, \text{CN}, \text{or Cl}$; $R_3 = \text{CF}_3 \text{ or } \text{CH}_3$; $R_4 = \text{H}, \text{Cl}, \text{F}, \text{NO}_2, \text{CN}, \text{MeO}, \text{or MeS}$; $X = \text{S}, \text{SO}, \text{or SO}_2$; and $R = \text{alkyl or heterocyclic derivs.}$) were prepared and tested for antiandrogen activity by their effects on accessory sex organs in rats. A series of compds. where $R_3 = \text{CF}_3$ generally exhibited partial androgen agonist activity, whereas those compds. where $R_3 = \text{CH}_3$ were pure antagonists. Optimization of the latter series of compds. led to novel, potent antiandrogens which were peripherally selective.

ST nonsteroidal antiandrogen structure activity; hydroxypropionanilide antiandrogen structure activity

IT Androgens

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor, thiohydroxypropionanilide derivs. as)

IT Molecular structure-biological activity relationship (androgen-inhibiting, of thiohydroxypropionanilide derivs.)

IT 95-76-1 100-01-6, reactions 393-11-3 635-22-3 654-70-6
825-41-2 20925-27-3 72115-06-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling of, with α -hydroxy acid chloride in dimethylacetamide)

IT 90357-42-9P 112988-42-8P 112988-43-9P 112988-44-0P 112988-45-1P
112988-46-2P 112988-47-3P 112988-48-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation and acid hydrolysis of)

IT 5042-53-5P 14109-72-9P 17078-37-4P 20996-62-7P 25784-83-2P
34509-09-6P 92682-40-1P 112988-41-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation and addition reaction of, with cyanide)

IT 112988-50-8DP, derivs.
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and antiandrogen activity of)

IT 90356-00-6P 90356-01-7P 90356-03-9P 90356-06-2P 90356-09-5P
90356-10-8P 90356-13-1P 90356-15-3P 90356-16-4P 90356-20-0P
90356-28-8P 90356-29-9P 90356-33-5P 90356-35-7P 90356-36-8P
90356-37-9P 90356-38-0P 90356-39-1P 90356-40-4P 90356-41-5P
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90356-62-0P 90356-63-1P 90356-64-2P 90356-70-0P 90356-71-1P
90356-72-2P 90356-74-4P 90356-75-5P 90356-76-6P 90356-77-7P
90356-78-8P 90356-79-9P 90356-80-2P 90356-81-3P 90356-83-5P
90356-87-9P 90356-88-0P 90356-92-6P 90356-93-7P 90356-98-2P
90356-99-3P 90357-00-9P 90357-02-1P 90357-03-2P 90357-04-3P
90357-05-4P 90357-06-5P 90357-07-6P 90357-09-8P
90357-19-0P 112988-36-0P 112988-37-1P 112988-38-2P 112988-39-3P
112988-40-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and antiandrogen activity of, structure in relation to)

IT 90357-22-5P 90357-26-9P 90357-27-0P 90357-28-1P 90357-29-2P
90357-34-9P 90357-35-0P 112988-49-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation and coupling of, with aniline in dimethylacetamide)

IT 90357-52-1P 90357-53-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation and epoxidn. of)

IT 90357-50-9P 90357-51-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation and reaction of, with thiols)

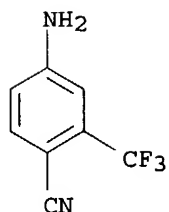
IT 74-93-1, reactions 75-08-1 75-33-2 106-54-7 107-03-9 108-98-5,
reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with bromoacetone and bromotrifluoroacetone)

IT 75-66-1 110-66-7 149-30-4 371-42-6 696-63-9 1122-97-0
1450-85-7 1849-36-1 2037-31-2 2637-34-5 4556-23-4 5685-05-2
5685-06-3 6320-03-2 7774-74-5 16133-26-9 29490-19-5 36801-01-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with epoxides)

IT 431-35-6, Bromotrifluoroacetone 598-31-2, Bromoacetone
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with thiols)

IT 654-70-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling of, with α -hydroxy acid chloride in dimethylacetamide)

RN 654-70-6 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



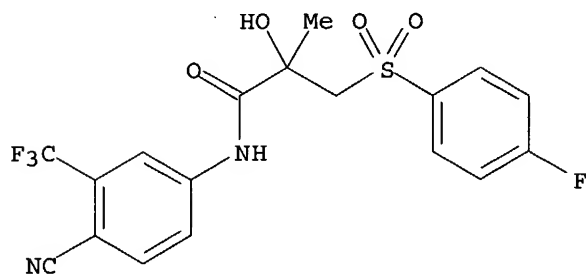
IT 90357-06-5P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation and antiandrogen activity of, structure in relation to)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



L71 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1988:150026 HCAPLUS

DN 108:150026

ED Entered STN: 30 Apr 1988

TI Resolution of the non-steroidal antiandrogen 4'-cyano-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide and the determination of the absolute configuration of the active enantiomer

AU Tucker, Howard; Chesterson, Glynne J.

CS Pharm. Div., Imp. Chem. Ind. PLC, Mereside/Macclesfield/Cheshire, SK10 4TG, UK

SO Journal of Medicinal Chemistry (1988), 31(4), 885-7
CODEN: JMCMAR; ISSN: 0022-2623

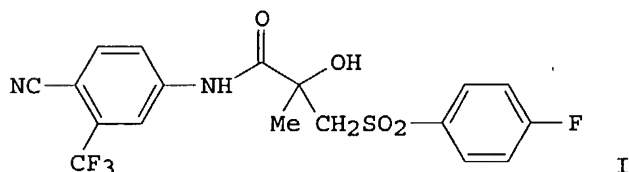
DT Journal

LA English

CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1

OS CASREACT 108:150026

GI



AB The nonsteroidal antiandrogen 4'-cyano-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide (I) has been resolved by chromatog. separation of the diastereomeric (R)-camphanil esters of the precursor thioether followed by hydrolysis and oxidation of the isolated enantiomers. In addition, an asym. synthesis of (S)-3-bromo-2-hydroxy-2-methylpropanoic acid and subsequent conversion into the (S)-sulfone has established that the more potent enantiomer of I has the R absolute configuration.

ST cyanotrifluoromethylpropionanilide fluorophenylsulfonyl resolu
antiandrogen

IT Androgens
RL: USES (Uses)
(inhibitors, cyanotrifluoromethyl(fluorophenylsulfonyl)propionanilide derivative)

IT Resolution
(of cyanotrifluoromethyl(fluorophenylsulfonyl)chloropropionyl derivative)

IT 51161-88-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(bromination of)

IT 371-42-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyanoetherification of)

IT 90357-17-8P 113299-38-0P 113299-40-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and antiandrogen activity of)

IT 113181-02-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and cyanoetherification of)

IT 106089-19-4P 113181-03-6P 113299-39-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)

IT 106089-20-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, chlorination, and amidation of)

IT 90357-18-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, oxidation, and antiandrogen activity of)

IT 90356-78-8
RL: PROC (Process)
(resolution of)

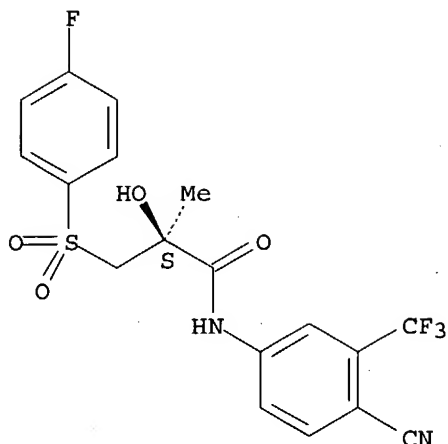
IT 654-70-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-acylation of)

IT 113299-38-0P 113299-40-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and antiandrogen activity of)

RN 113299-38-0 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

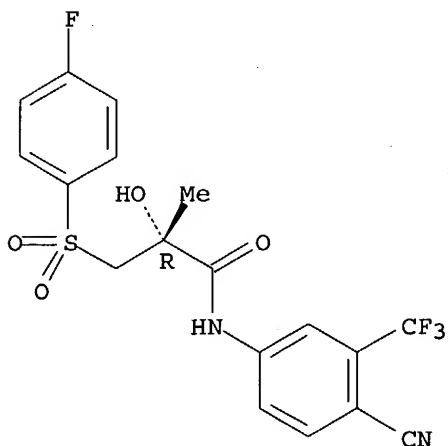
Absolute stereochemistry. Rotation (+).



RN 113299-40-4 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

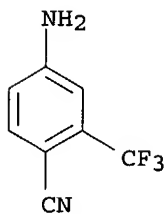


IT 654-70-6

RL: RCT (Reactant); RACT (Reactant or reagent)
(N-acylation of)

RN 654-70-6 HCAPLUS

CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)

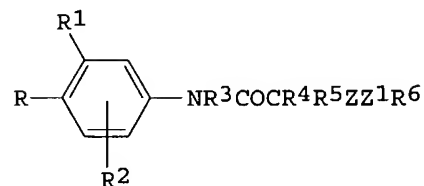


DN 101:54739
 ED Entered STN: 18 Aug 1984
 TI Amide derivatives
 IN Tucker, Howard
 PA Imperial Chemical Industries PLC, UK
 SO Eur. Pat. Appl., 53 pp.
 CODEN: EPXXDW
 DT Patent
 LA English
 IC C07C149-23; C07C149-41; C07C103-375; C07C103-50; C07C121-78; C07C147-107;
 C07C147-14; C07D213-70; C07D247-02; C07D283-02; C07D285-12
 CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 100172	A1	19840208	EP 1983-303998	19830708 <--
	EP 100172	B1	19870812		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	AT 28864	E	19870815	AT 1983-303998	19830708 <--
	IL 69217	A1	19870331	IL 1983-69217	19830713 <--
	ZA 8305182	A	19840530	ZA 1983-5182	19830715 <--
	US 4636505	A	19870113	US 1983-514332	19830715 <--
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	NO 164974	C	19901205		
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	AU 556328	B2	19861030		
	HU 32058	O	19840628	HU 1983-2531	19830718 <--
	HU 191296	B	19870227		
	FI 8302644	A	19840124	FI 1983-2644	19830720 <--
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	FI 83770	C	19910826		
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	JP 04032061	B4	19920528		
	CA 1249823	A1	19890207	CA 1983-432811	19830720 <--
	ES 524392	A1	19851101	ES 1983-524392	19830722 <--
	ES 539614	A1	19860601	ES 1985-539614	19850116 <--
	ES 539615	A1	19860601	ES 1985-539615	19850116 <--
	ES 544189	A1	19860916	ES 1985-544189	19850614 <--
	JP 02131462	A2	19900521	JP 1989-230574	19890907 <--
PRAI	GB 1982-21421		19820723		<--
	EP 1983-303998		19830708		<--

GI



I

AB Antiandrogenic (no data) alkananilides including I [R = alkanoyl, halo, cyano, NO₂, alkylthio, alkylsulfinyl, alkylsulfonyl, PhS, PhSO, PhSO₂, etc.; R¹ = H, alkyl, alkoxy, R; R² = H, halo; R³ = H, alkyl; R⁴ = H, OH, alkoxy, acyloxy; R⁵ = alkyl, haloalkyl; R⁴R⁵ = CO₂; R⁶ = (un)substituted alkyl, alkenyl, Ph, naphthyl, heterocyclyl; Z = bond, alkylene; Z¹ = O, S,

S(O), SO₂, NR7; R7 = H, alkyl] (124 compds.) were prepared Thus, Me 2,3-epoxy-2-methylpropionate, prepared by epoxidn. of H₂C:CM₂CO₂Me, was treated with NaH and PhSH to give PhSCH₂CM₂(OH)CO₂Me. This was saponified to give the free acid which was treated with SOCl₂ and 4,3-(NC)(F₃C)C₆H₃NHCOCMe(OH)CH₂SPh.

- ST antiandrogenic phenylthiohydroxypropionanilide; propionanilide hydroxy phenylthio; aniline alkanoylation; glycidate alkanethiol benzenethiol
- IT Androgens
RL: USES (Uses)
(inhibitors, hydroxypropionanilides)
- IT 80-59-1 565-63-9 920-46-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation by, of anilines)
- IT 95-76-1 393-11-3 635-22-3 654-70-6 825-41-2 7251-09-4
20925-27-3 56765-79-8 72115-06-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation of, by glycidates and hydroxypropionates)
- IT 431-35-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation by, of thiols)
- IT 87310-62-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with Me Ph sulfide and (methylsulfonyl)thiophene)
- IT 74-93-1, reactions 75-33-2 100-53-8 107-03-9 1849-36-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with bromotrifluoroacetone)
- IT 60-24-2 60-56-0 75-08-1 96-53-7 106-54-7 108-98-5, reactions
110-66-7 149-30-4 371-42-6 696-63-9 870-23-5 1122-97-0
1450-85-7 1679-07-8 2037-31-2 2637-34-5 4556-23-4 5685-05-2
5685-06-3 5954-68-7 6320-03-2 7774-74-5 16133-26-9 29490-19-5
36801-01-1 40771-41-3 67131-59-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with glycidates)
- IT 100-68-5 90357-57-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with pyruvanilide)
- IT 58653-97-7P 65925-77-1P 90357-50-9P 90357-51-0P 90357-56-5P
90366-53-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and condensation of, with thiols)
- IT 90357-14-5P 90410-51-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and decomposition of)
- IT 2164-09-2P 90357-52-1P 90357-53-2P 90357-54-3P 90357-55-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and epoxidn. of)
- IT 34509-09-6P 90357-44-1P 90357-45-2P 90357-46-3P 90357-47-4P
90357-48-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrocyanation of)
- IT 90357-42-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)
- IT 90356-00-6P 90356-01-7P 90356-04-0P 90356-05-1P 90356-07-3P
90356-08-4P 90356-14-2P 90356-17-5P 90356-18-6P 90356-19-7P
90356-38-0P 90356-60-8P 90356-70-0P 90356-78-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and oxidation of)

IT 64454-43-9P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and saponification of)

IT	90356-02-8P	90356-03-9P	90356-06-2P	90356-09-5P	90356-10-8P
	90356-11-9P	90356-12-0P	90356-13-1P	90356-15-3P	90356-16-4P
	90356-20-0P	90356-21-1P	90356-22-2P	90356-23-3P	90356-24-4P
	90356-25-5P	90356-26-6P	90356-27-7P	90356-28-8P	90356-29-9P
	90356-30-2P	90356-31-3P	90356-32-4P	90356-33-5P	90356-34-6P
	90356-35-7P	90356-36-8P	90356-37-9P	90356-39-1P	90356-40-4P
	90356-41-5P	90356-42-6P	90356-43-7P	90356-44-8P	90356-45-9P
	90356-46-0P	90356-47-1P	90356-48-2P	90356-49-3P	90356-50-6P
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	90356-56-2P	90356-57-3P	90356-58-4P	90356-59-5P	90356-61-9P
	90356-62-0P	90356-63-1P	90356-64-2P	90356-65-3P	90356-66-4P
	90356-67-5P	90356-68-6P	90356-69-7P	90356-71-1P	90356-72-2P
	90356-73-3P	90356-74-4P	90356-75-5P	90356-76-6P	90356-77-7P
	90356-79-9P	90356-80-2P	90356-81-3P	90356-82-4P	90356-83-5P
	90356-84-6P	90356-85-7P	90356-86-8P	90356-87-9P	90356-88-0P
	90356-89-1P	90356-90-4P	90356-91-5P	90356-92-6P	90356-93-7P
	90356-94-8P	90356-95-9P	90356-96-0P	90356-97-1P	90356-98-2P
	90356-99-3P	90357-00-9P	90357-01-0P	90357-02-1P	90357-03-2P
	90357-04-3P	90357-05-4P	90357-06-5P	90357-07-6P	
	90357-08-7P	90357-09-8P	90357-10-1P	90357-11-2P	90357-12-3P
	90357-13-4P	90357-15-6P	90357-16-7P	90357-17-8P	90357-18-9P
	90357-19-0P	90357-20-3P	90357-21-4P	90357-43-0P	90373-25-4P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of)

IT	90357-22-5P	90357-25-8P	90357-26-9P	90357-27-0P	90357-28-1P
	90357-29-2P	90357-30-5P	90357-31-6P	90357-32-7P	90357-33-8P
	90357-34-9P	90357-35-0P	90357-36-1P	90357-37-2P	90357-38-3P
	90357-39-4P	90357-40-7P	90357-41-8P		

RL: SPN (Synthetic preparation); PREP (Preparation)

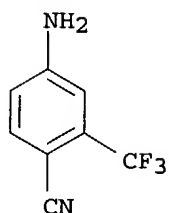
(preparation of, and acylation of anilines by)

IT 654-70-6
 RL: RCT (Reactant); RACT (Reactant or reagent)

(acylation of, by glycidates and hydroxypropionates)

RN 654-70-6 HCAPLUS

CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)

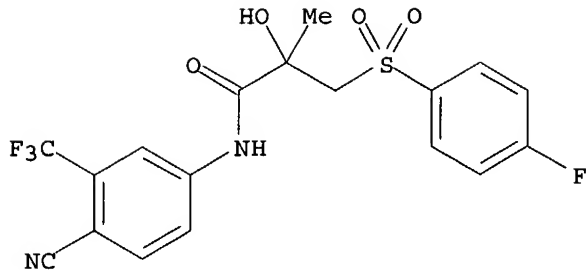


IT 90357-06-5P
 RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



=> fil wpix

FILE 'WPIX' ENTERED AT 10:06:56 ON 02 JUN 2004

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 MOST RECENT DERWENT UPDATE: 200434 <200434/DW>
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L92 ANSWER 1 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
 AN 2004-339374 [31] WPIX
 DNC C2004-128760
 TI New polymorphic forms of **bicalutamide** useful in the treatment of
 e.g. prostate cancer.
 DC A96 B05
 IN WESTHEIM, R J H
 PA (WEST-I) WESTHEIM R J H; (SYNT-N) SYNTHON BV

CYC 105

PI US 2004063782 A1 20040401 (200431)* 15 A61K031-277
WO 2004029021 A1 20040408 (200431) EN C07C317-46
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
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DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC
VN YU ZA ZM ZW

ADT US 2004063782 A1 Provisional US 2002-413765P 20020927, Provisional US
2003-470223P 20030514, US 2003-660775 20030912; WO 2004029021 A1 WO
2003-EP10933 20030925

PRAI US 2003-660775 20030912; US 2002-413765P 20020927;
US 2003-470223P 20030514

IC ICM A61K031-277; C07C317-46

AB US2004063782 A UPAB: 20040514

NOVELTY - Polymorphic forms including **crystalline** form (II) (A1)
and amorphous form (B1) of **bicalutamide** are new.

DETAILED DESCRIPTION - Polymorphic forms including
crystalline form (II) (A1) and amorphous form (B1) of
bicalutamide are new.

INDEPENDENT CLAIMS are included for following

- (1) a composition (C1) comprising (A1), at least one of
crystalline bicalutamide of form (I), and (B1);
- (2) a composition (C2) comprising (A1), and an excipient; and
- (3) preparation of the polymorphic forms.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Androgenic inhibitor.

USE - For treating prostate cancer and having anti-androgenic
activity.

ADVANTAGE - The **bicalutamide** of form (II) is isolated in a
relatively pure form with at least 98% purity. The polymorphic forms
exhibit better stability than the prior art excellent antiandrogenic
activity and hence are effective for treating prostate cancer.

Dwg.0/8

FS CPI

FA AB; DCN

MC CPI: A12-V01; B04-C02A1; B04-C02A2; B04-C02B2; B07-A02B; B10-A10;
B14-D02A; B14-H01; B14-N07A

TECH UPTX: 20040514

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation
of (A1) involves:

(a) Process A: precipitating (A1) from a solution containing
bicalutamide in the presence of seed **crystals** of form
(II) by lowering the temperature of the solution and/or contacting with a
contrasolvent at least 35 degrees C; and

(b) Process B: heating (B1) to get **crystals** of (A1).

Preparation of (B1) involves heating a solid form of **bicalutamide**
to form a melt and cooling the resultant melt.

Preferred Components: Form (II) is characterized by an X-ray diffraction
pattern as given in the specification. The **crystalline** form is
racemic. The excipient is a carrier or diluent (preferably
microcrystalline cellulose, hydroxypropyl methylcellulose, lactose
or starch).

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The
excipient is calcium phosphate.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: (C2) Comprises
form (II) (0.1 - 99.9 wt.%). (C2) Is substantially free of the form (I),
but optionally comprises the form (I). (C2) Is in an unit dose formulated
as solid oral dosage form, solution or suspension.

ABEX

UPTX: 20040514

ADMINISTRATION - Administration of (A1) is orally (claimed). Dosage is 0.1 - 125 mg/kg or 1 - 600 (preferably 1 - 300, especially 50 - 150) mg.

EXAMPLE - **Bicalutamide** form (I) (1 g) was heated in an oil bath at 210 degrees C for 5 minutes. The resultant melt was cooled to room temperature; and again heated in the oil bath at 160 degrees C. Within few minutes **crystals** of **bicalutamide** form (II) were formed. The resultant **crystals** (5 mg) were suspended in n-heptane (7 ml) and the suspension was stirred with a magnetic stirrer in a water bath. **Bicalutamide** form (I) (0.5 g) was dissolved in ethyl acetate (7 ml) at reflux. The warm solution was added dropwise to the stirred cold heptane suspension. The resultant milky suspension was filtered under reduced pressure, and dried at ambient temperature under vacuum for 1.5 hours. **Bicalutamide** (190 g) was dissolved in ethyl acetate (2.52 ml) at reflux, and was added to n-heptane (3 ml) which was cooled to -5 to -10 degrees C and seeded with the form (I) (200 mg). The resultant suspension was stirred for 5 minutes, filtered, washed with cold n-heptane, and dried to get **crystalline bicalutamide** form (II) (160 g, 99.78% purity).

L92 ANSWER 2 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2004-248621 [24] WPIX

DNC C2004-097261

TI **Casodex** synthesizing process for anti-tumour medicine.

DC B05

IN LU, W; XIA, Y; ZHU, Q

PA (SHAN-N) SHANGHAI MEDICINE INST CHINESE ACAD SCI

CYC 1

PI CN 1458146 A 20031126 (200424)* C07C317-32

ADT CN 1458146 A CN 2002-111681 20020515

PRAI CN 2002-111681 20020515

IC ICM C07C317-32

ICS A61P035-00; C07C315-02

AB CN 1458146 A UPAB: 20040408

NOVELTY - The present invention provides the new synthesis process of **Casodex** as a kind of antitumor medicine. During the synthesis of **Casodex**, it is needed to oxidize thioether intermediate into sulfone, and available industrial oxidation process adopts acid peroxide as oxidant, which is expensive, explosive and pollutant. The present invention uses hydrogen peroxide as oxidant and produces the product through reaction in proper solvent, in the presence of catalyst and at certain temperature. The present invention has high product yield and purity, no any environmental pollution, simple operation and treatment, and is suitable for industrial production.

Dwg.0/0

FS CPI

FA AB

MC CPI: B10-B04A; B10-H02; B14-H01

L92 ANSWER 3 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2004-118871 [12] WPIX

CR 2004-315002 [29]

DNC C2004-047589

TI Preparation of **bicalutamide**, useful for treating prostate cancer and other androgen dependent conditions, comprises reacting 4-fluorobenzene sulfinic acid salt with reaction partner..

DC B05

IN ETTEMA, G J B; KELTJENS, R; THIJS, L

PA (SYNT-N) SYNTHON BV

CYC 105

PI US 2003073742 A1 20030417 (200412)* 24 A61K031-277

WO 2004031136 A1 20040415 (200426) EN C07C315-00 <--

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LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC
VN YU ZA ZM ZW

ADT US 2003073742 A1 US 2002-261492 20021002; WO 2004031136 A1 WO 2003-EP11166
20031001

PRAI US 2002-261492 20021002

IC ICM A61K031-277; C07C315-00

ICS C07C315-04; C07C317-32; C07C317-46

AB US2003073742 A UPAB: 20040505

NOVELTY - Preparation of **bicalutamide** (I) comprises reacting a 4-fluorobenzene sulfinic acid salt (II) with a reaction partner to form (I) and a non **bicalutamide** product (II) and converting (II) to (I).

DETAILED DESCRIPTION - Preparation of **bicalutamide** (I) comprises reacting a 4-fluorobenzene sulfinic acid salt of formula (II) with a reaction partner to form (I) and a non **bicalutamide** product (II) and converting (II) to (I).

Z = a cation.

An INDEPENDENT CLAIM is also included for new compounds of formula (IV).

A = OR;

X = H, or

A + X = 5-10 membered optionally fused heterocyclyl, and

R = 1-6C alkyl, 3-6C cycloalkyl, phenyl or benzyl,

provided that if a ring N atom is present, it is optionally substituted by 3-trifluoromethyl-4-cyanophenyl.

ACTIVITY - Cytostatic.

No biological data available.

MECHANISM OF ACTION - Androgen inhibitor.

USE - Used as a non-steroidal antiandrogen agent used in the treatment of prostate cancer and other androgen dependent conditions.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-H; B10-A10; B14-D02; B14-H01; B14-L06

TECH UPTX: 20040218

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: The reaction partner comprises Y-CH₂-C(Me)(OX₁)-COA₁, L-CH₂-C(Me)=CH₂ or L-CH₂-COMe.

A₁ = OR or 3-trifluoromethyl-4-cyanophenylamino;

Y = a leaving group;

X₁ = H, or

X₁ + Y = 3-6 membered heterocyclyl, or

X₁ + A₁ = 5- or 6-membered heterocyclyl, and

L = halo.

(II) Is reacted with Y₁-CH₂-C(Me)(OX₂)-COA₂ to form a compound of formula (IVA).

Y₁ = a leaving group;

A₂ = OR or 3-trifluoromethyl-4-cyanophenylamino, and

X₂ = H, or

X₂ + Y₁ = 3-6 membered heterocyclyl, or

X₂ + A₂ = 5-10 membered optionally fused heterocyclyl,

Provided that if a ring N atom is present, it is optionally substituted by 3-trifluoromethyl-4-cyanophenyl.

Reaction of (II) with a reaction partner is effected in a biphasic reaction system or in a lower alcohol. A₂ is 3-trifluoromethyl-4-cyanophenylamino and (IVA) is (I). Y₁-CH₂-C(Me)(OX₂)-COA₂ is optically active and (I) is enriched R-(I). (I) Is racemic and R-(I) isomer is isolated.

ABEX UPTX: 20040218

EXAMPLE - In a flask (25 ml) with a magnetic stirrer, N-(4-cyano-3-

(trifluoromethyl)phenyl)-2-hydroxy-3-iodo-2-methylpropanamide (0.200 g) and sodium p-fluorobenzenesulfinate (0.2 g) were dissolved in dimethylsulfoxide (3-4 ml) and heated at 60 degrees C for 18 hours. During the reaction, the next three portions of sodium p-fluorobenzenesulfinate (0.200 g) were added. The reaction was followed by high performance liquid chromatography analysis. To the reaction mixture was added ethyl acetate (30 ml), brine (30 ml) and water (20 ml). The organic layer was washed with 0.5N aqueous HCl (20 ml), water (20 ml) and saturated aqueous NaHCO₃ (20 ml). After drying (Na₂SO₄) and concentration in vacuo, the crude product was purified by column chromatography (Merck60 SiO₂; eluent = ethyl acetate/heptane = 3/2) to give **bicalutamide** (0.050 g; 23%).

DEFINITIONS - Preferred Definitions:

Z = alkali metal, Mg halide or ammonium.

L92 ANSWER 4 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-012518 [01] WPIX
DNC C2004-003809
TI Pure **bicalutamide** preparation, useful as antiandrogen in treating prostate cancer, from epoxide or halohydrin (or their precursors) and p-fluorophenylsulfinate salt.
DC B05
IN BOR, A; LUKACS, F; OROSZ, G; SCHNEIDER, G
PA (CFPH-N) CF PHARMA GYOGYSZERGYARTO KFT; (HELM-N) HELM AG
CYC 103
PI WO 2003097590 A1 20031127 (200401)* GE 26 C07C315-00 <--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
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DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL
PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU
ZA ZM ZW
DE 10222104 A1 20031204 (200401) C07C315-00 <--
ADT WO 2003097590 A1 WO 2003-EP4999 20030513; DE 10222104 A1 DE 2002-10222104
20020517
PRAI DE 2002-10222104 20020517
IC ICM C07C315-00
ICS C07C317-46
AB WO2003097590 A UPAB: 20040102
NOVELTY - Preparation of N-(4-cyano-3-trifluoromethyl-phenyl)-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methyl-propionamide (I) involves reacting N-(4-cyano-3-trifluoromethyl-2-methyl-oxirane-2-carboxamide or a corresponding halohydrin (or their precursors) with a p-fluorophenylsulfinate salt (IV) and if necessary converting the precursor residue.
DETAILED DESCRIPTION - Preparation of N-(4-cyano-3-trifluoromethyl-phenyl)-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methyl-propionamide of formula (I) involves reacting an epoxide of formula (II) or a halohydrin (or analog) of formula (III) with a p-fluorophenylsulfinate salt (IV) and if necessary converting a precursor group R into N-(4-cyano-3-trifluoromethyl-phenyl)-aminocarbonyl.
R = N-(4-cyano-3-trifluoromethyl-phenyl)-aminocarbonyl or its precursor;
X = leaving group.
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - None given.
USE - (I) is an antiandrogen useful in the treatment of prostate carcinoma.
ADVANTAGE - Racemic or enantiomeric (I) is obtained in pharmaceutically acceptable purity by a simple and economical procedure, using (IV) as starting material (rather than the highly toxic

p-fluorothiophenol plus expensive and/or dangerous oxidizing agents as in prior art methods).

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B10-A10; B14-D02A; B14-H01

TECH UPTX: 20040102

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: (II) is obtained from (III), conversion of (III) to (II) and reaction of (II) with (IV) preferably being carried out as a one-pot reaction. (II) or (III) is racemic or optically active R- or S-enantiomer form. (IV) is an alkali metal p-fluorophenylsulfinate, preferably the sodium salt.

ABEX UPTX: 20040102

SPECIFIC COMPOUNDS - (I) is specifically disclosed as **bicalutamide**

EXAMPLE - A mixture of 7.0 g N-(4-cyano-3-trifluoromethyl-phenyl)-2-methyl-oxirane-2-carboxamide, 9.43 g sodium p-fluorophenylsulfinate, 50 ml methanol and 3 ml glacial acetic acid was heated under reflux for 5 hours, then evaporated. The residue was partitioned between dichloromethane and water, and the organic phase was washed, dried and evaporated. The residue was **recrystallized** from diisopropyl ether to give 7.1 g of **bicalutamide**, m.pt. 187-189 degrees C, purity 96.6% (by HPLC).

DEFINITIONS - Preferred Definitions:

R = N-(4-cyano-3-trifluoromethyl-phenyl)-aminocarbonyl or -CO-Y;

X = halo (e.g. Cl, Br or I) or alkyl- or arylsulfonate (e.g. mesylate, tosylate or brosylate).

L92 ANSWER 5 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-607903 [57] WPIX

DNC C2003-165631

TI Preparation of **bicalutamide** from N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline and monohypophthalic acid.

DC B05

IN ITAYA, N; KATSURA, T; SHINTAKU, T

PA (ITAY-I) ITAYA N; (KATS-I) KATSURA T; (SHIN-I) SHINTAKU T; (SUMO) SUMIKA
FINE CHEM CO LTD

CYC 101

PI WO 2003053920 A1 20030703 (200357)* JA 46 C07C315-02 <--

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU

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RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM

ZW

US 2003191337 A1 20031009 (200367) C07C317-34

AU 2002354475 A1 20030709 (200428) C07C315-02 <--

ADT WO 2003053920 A1 WO 2002-JP13058 20021213; US 2003191337 A1 WO
2002-JP13058 20021213, US 2003-362410 20030224; AU 2002354475 A1 AU
2002-354475 20021213

FDT AU 2002354475 A1 Based on WO 2003053920

PRAI JP 2002-166213 20020606; JP 2001-380686 20011213

IC ICM C07C315-02; C07C317-34

ICS A61K031-277; A61K031-2777; A61P005-28; A61P005-288; A61P043-00;

A61P043-000; C07C315-06; C07C315-066; C07C317-46;

C07C317-466

AB WO2003053920 A UPAB: 20030906

NOVELTY - Preparation of **bicalutamide** (I) includes the step of reacting N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline (II) with monoperphthalic acid to give 4-cyano-N-(2,3-epoxy-2-methylpropionyl)-3-trifluoromethylaniline (III).

DETAILED DESCRIPTION - Preparation of **bicalutamide** of formula (I) includes the step of reacting N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline of formula (II) with monoperphthalic acid to give 4-cyano-N-(2,3-epoxy-2-methylpropionyl)-3-trifluoromethylaniline of formula (III).

INDEPENDENT CLAIMS are also included for:

(1) preparation of (I) which includes the step of reacting 4'-cyano-3-(4-fluorophenylthio)-2-hydroxy-2-methyl-3'-trifluoromethylpropionanilide of formula (IV) either with monoperphthalic acid or with hydrogen peroxide in the presence of a sodium tungstenate or its solvate, phenylsulfonic acid or a phase transfer catalyst in ethyl acetate;

(2) preparation of **crystalline** (I) comprising dissolving (I) in ethyl acetate, adding hexane, heptane or a similar hydrocarbon solvent, and **crystallizing** (I) from the solvent mixture; and

(3) **crystalline** (I) having ¹³C-NMR data given in the specification.

USE - For preparing **bicalutamide** preferably in **crystalline** form useful as an antiandrogenic agent.

ADVANTAGE - Processes are environmentally friendly, economical, efficient and safe.

Dwg.0/1

FS

CPI

FA

AB; GI; DCN

MC

CPI: B05-A01B; B05-A03B; B07-A03; B10-A10; B10-A15; B14-D02

TECH

UPTX: 20030906

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: (IV) Is oxidized is using 3-6 moles hydrogen peroxide per mole of (IV) in the presence of 0.5-5 moles of catalyst.

ABEX

UPTX: 20030906

EXAMPLE - Monoperphthalic acid (108.05 g, then 19.82 g) was added to N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline (II) (13.8 g) in ethyl acetate at 50-55 degrees C and the mixture was stirred at 50-55 degrees C for 3.9 hours. Monoperphthalic acid (10.36 g, then 1.90 g) was added and the mixture was reacted for a further hour. Work-up gave 4-cyano-N-(2,3-epoxy-2-methylpropionyl)-3-trifluoromethylaniline (III) (11.37 g; 77.3 % yield; 98.7 % purity).

L92

ANSWER 6 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN

2003-156908 [15] WPIX

DNC

C2003-040799

TI

Preparation of rac-**bicalutamide** useful for selectively reducing testosterone level, comprising addition of ethyl-(2-(4-fluorophenyl sulfone))-2-hydroxy propionic acid to 5-amino-2-cyano-benzotrifluoride and butyl lithium in organic solvent.

DC

B05

IN

DOLITZKY, B; REANY, O; SHAMMAI, J;
SHAMAI, J

PA

(BIOG) BIOGAL GYOGYSZERGYAR; (DOLI-I) DOLITZKY B; (REAN-I) REANY O; (SHAM-I) SHAMMAI J; (BIOG) BIOGAL GYOGYSZERGYAR RT; (TEVA-N) TEVA PHARM IND LTD; (TEVA-N) TEVA PHARM USA INC

CYC

101

PI

WO 2002100339 A2 20021219 (200315)* EN 11 A61K000-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
ZW

US 2003045741 A1 20030306 (200320)

C07C315-04 <--

US 2004044249 A1 20040304 (200417)

C07C317-28 <--

US 2004059147 A1 20040325 (200422)

C07C317-24

EP 1406855 A2 20040414 (200426) EN C07C069-675
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 US 6737550 B2 20040518 (200433) C07C315-04 <--
 ADT WO 2002100339 A2 WO 2002-US18329 20020613; US 2003045741 A1
 Provisional US 2001-298009P 20010613, Provisional US
 2002-371069P 20020409, US 2002-170721 20020613; US 2004044249 A1
 Provisional US 2001-298009P 20010613, Provisional US
 2002-371069P 20020409, CIP of US 2002-170721 20020613, US 2003-606403
 20030625; US 2004059147 A1 Provisional US 2001-298009P 20010613,
 Provisional US 2002-371069P 20020409, Div ex US 2002-170721
 20020613, US 2003-668982 20030922; EP 1406855 A2 EP 2002-739801 20020613,
 WO 2002-US18329 20020613; US 6737550 B2 Provisional US
 2001-298009P 20010613, Provisional US 2002-371069P 20020409
 , US 2002-170721 20020613
 FDT EP 1406855 A2 Based on WO 2002100339
 PRAI US 2002-371069P 20020409; US 2001-298009P
 20010613; US 2002-170721 20020613; US 2003-606403
 20030625; US 2003-668982 20030922
 IC ICM A61K000-00; C07C069-675; C07C315-04; C07C317-24; C07C317-28
 ICS C07C255-49; C07C255-50; C07C317-14
 AB WO2002100339 A UPAB: 20030303

NOVELTY - Preparation (P1) of rac-bicalutamide (I) (both R- and S- isomers) comprises addition of ethyl-(2-(4-fluorophenyl sulfone))-2-hydroxy propionic acid (i) to a mixture of 5-amino-2-cyano-benzotrifluoride and butyl lithium in an organic solvent, and recovering.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) a rac-bicalutamide intermediate of formula (X) or (Y), which represent stable organo lithium salts of 4-fluorophenyl methyl sulfone and 5-amino-2-cyano-benzotrifluoride, respectively;
- (2) preparation (P2) of the intermediates comprising addition of butyl lithium to a solution of a substrate (S1 or S2 representing 4-fluorophenyl methyl sulfone and 5-amino-2-cyano-benzotrifluoride for (X) and (Y) preparation, respectively) in the organic solvent.
- (3) preparation (P3) of methyl 2,3-epoxy-2-methyl propionate comprising addition of methyl methacrylate to oxone dissolved in a basic solution, followed by addition of an acid;
- (4) preparation (P4) of 2-hydroxy-2-methyl-3-(4-fluorophenylthio)propionic acid comprising addition of methyl-1,2-epoxy-2-methyl propionate to a solution of 4-fluorothiophenol in methanol, followed by addition of ethyl acetate and recovering the product;
- (5) preparation of ethyl-(2-(4-fluorophenyl sulfone))-2-hydroxy propionate comprising addition of ethyl pyruvate to a mixture of 4-fluorophenyl methyl sulfone and butyl lithium in an organic solvent followed by recovering; and

- (6) micronized (I) having a mean particle diameter of less than 200 μ m (preferably less than 100 μ m, especially less than 10 μ m).

ACTIVITY - None given in the source material.

MECHANISM OF ACTION - None given in the source material.

USE - Micronized (I) is used for preparation of a composition (claimed) useful for selectively reducing the testosterone level.

ADVANTAGE - The processes are economical, environmentally safe and feasible. The process is simple without involvement of any dangerous oxidizing compounds such as meta-chloroperbenzoic acid. The mean particle size of (I) provides an improved, reproducible and stable dissolution profile. (I) Also has an anti-androgen activity and selectively decreases the testosterone level without influencing the regulation mechanisms of the hypothalamus. (I) (Particularly the (R) isomer) is more active having lesser side effects such as headache and giddiness.

Dwg.0/2

FS CPI
FA AB; DCN
MC CPI: B10-A10; B10-A15; B10-C04B; B14-D02A
TECH UPTX: 20030303

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The basic solution is potassium hydroxide or sodium hydroxide (preferably 10M potassium hydroxide for (P3) and 2N sodium hydroxide for (P4)). Oxone is potassium hydrogen sulfate (KHSO5) (50%). The acid is hydrochloric, nitric or phosphoric acid (preferably 0.05 - 5 N hydrochloric acid). Preferred Process: In (P1), (i) is added to the mixture at -65 degrees C. (I) Is obtained by evaporating a reaction mixture, preferably separating (i). In (P2), butyl lithium reacts with the substrate in the presence of an anion stabilizer (preferably 1,4-diazabicyclo(2.2.2)octane) at -40 to 10 (preferably -2 to 2) degrees C. In (P3), methyl methacrylate is added in methanol and the oxone solution containing the methyl methacrylate is maintained at pH 6. In (P4), the 4-fluorothiophenol solution is prepared by adding the basic solution under N2 flow. The reaction mixture in (P4) is obtained by stirring at room temperature for 90 minutes. The recovery in (P4) is by extraction (preferably chloroform extraction) and further solidification of the product.

ABEX UPTX: 20030303
SPECIFIC COMPOUNDS - Tetrahydrofuran or diethyl ether are specifically claimed as the organic solvent.

ADMINISTRATION - The dosage of (I) is 2 - 200 (preferably 5 - 100) mg/day and is administered orally or intravenously.

EXAMPLE - 4-Fluorophenyl methyl sulfone (4-FPMS) (5 g) and 1,4-diazabicyclo(2.2.2)octane (3.2 g) (DABCO) were dissolved in tetrahydrofuran (THF) and cooled to -2 degrees C in dry-ice acetone bath. A butyl lithium solution (2.5 M) in hexane (14.5 ml) was added to the cold THF dropwise at -2 to 2 degrees C. The mixture was then stirred for 1 hour and then ethyl pyruvate solution (3.67 g) in THF (30 ml) was added to the mixture at -65 degrees C. The mixture was stirred for 1 hour at -65 to -30 degrees C. 2N hydrochloric acid (HCl) was then added to the reaction and the mixture was warmed to room temperature. The reaction mixture was evaporated in vacuo, after which the residue was extracted with diethyl ether (3 x 100 ml). The combined ether extracts were dried over sodium bisulfate (NaSO4), filtered and purified by column chromatography using dichloromethane to give rac-ethyl-(2-(4-fluorophenyl sulfone))-2-hydroxy propionate.

L92 ANSWER 7 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2002-339937 [37] WPIX

DNC C2002-097694

TI Preparation of N-phenyl-3-alkyl sulfonyl-2-hydroxy-2-alkylpropanamide derivatives e.g. **bicalutamide**, comprises reaction of substituted benzene and acrylamide derivative, epoxidizing, reacting with thiol and then oxidizing.

DC B05

IN CHEN, B; SUNDEEN, J E; ZHAO, R

PA (CHEN-I) CHEN B; (SUND-I) SUNDEEN J E; (ZHAO-I) ZHAO R; (BRIM)
BRISTOL-MYERS SQUIBB CO

CYC 98

PI WO 2002024638 A1 20020328 (200237)* EN 26 C07C317-46
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO
RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
US 2002086902 A1 20020704 (200247) C07C317-24
AU 2001095044 A 20020402 (200252) C07C317-46

US 6562994 B2 20030513 (200335) C07C255-00
 EP 1322603 A1 20030702 (200344) EN C07C317-46
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 CZ 2003000836 A3 20030813 (200357) C07C317-46
 KR 2003048408 A 20030619 (200369) C07C315-02 <--
 HU 2003002930 A2 20031229 (200413) C07C317-46
 JP 2004509164 W 20040325 (200422) 44 C07C315-02 <--
 ADT WO 2002024638 A1 WO 2001-US42171 20010917; US 2002086902 A1 Provisional US
 2000-234121P 20000921, US 2001-953759 20010917; AU 2001095044 A AU
 2001-95044 20010917; US 6562994 B2 Provisional US 2000-234121P 20000921,
 US 2001-953759 20010917; EP 1322603 A1 EP 2001-975752 20010917, WO
 2001-US42171 20010917; CZ 2003000836 A3 WO 2001-US42171 20010917, CZ
 2003-836 20010917; KR 2003048408 A KR 2003-704173 20030321; HU 2003002930
 A2 WO 2001-US42171 20010917, HU 2003-2930 20010917; JP 2004509164 W WO
 2001-US42171 20010917, JP 2002-529051 20010917
 FDT AU 2001095044 A Based on WO 2002024638; EP 1322603 A1 Based on WO
 2002024638; CZ 2003000836 A3 Based on WO 2002024638; HU 2003002930 A2
 Based on WO 2002024638; JP 2004509164 W Based on WO 2002024638
 PRAI US 2000-234121P 20000921; US 2001-953759 20010917
 IC ICM C07C255-00; C07C315-02; C07C317-24; C07C317-46
 ICS A61K031-16; A61K031-277; C07C231-08; C07C253-30; C07C255-60;
 C07C255-66; C07C315-00; C07C317-00; C07C319-14; C07C323-52;
 C07C323-62; C07D301-14; C07D301-16; C07D303-48
 AB WO 200224638 A UPAB: 20020613
 NOVELTY - Preparation of an N-(phenyl)-3-alkylsulfonyl-2-hydroxy-2-
 alkylpropanamide derivative (I) comprises reacting a substituted benzene
 derivative (II) with an alpha , beta -unsaturated propanamide derivative
 (III) in the presence of a first base followed by reaction with an
 epoxidizing agent, then with a thiol derivative in the presence of a
 second base and then reacting with an oxidizing agent.
 DETAILED DESCRIPTION - Preparation of an N-(phenyl)-3-alkylsulfonyl-2-
 hydroxy-2-alkylpropanamide derivative of formula (I) comprises:
 (a) reacting a substituted benzene derivative of formula (II) with an
 alpha , beta -unsaturated propanamide derivative of formula (III) in the
 presence of a first base to form an N-(substituted phenyl)- alpha , beta
 -unsaturated propanamide derivative of formula (IV);
 (b) reacting (IV) with an epoxidizing agent to form an epoxide of
 formula (V);
 (c) reacting (V) with a thiol of formula R2SH (VI) in the presence of
 a second base to form a sulfide of formula (VII); and
 (d) reacting (VII) with an oxidizing agent.
 Y' = T' or alkylsulfonyl;
 T' = cyano, nitro, perfluoroalkyl, alkylcarbonyl or alkoxy; carbonyl;
 R = T', alkyl or alkoxy;
 R1 = (halo)alkyl;
 R2 = alkyl or (hetero)aryl;
 X = F, Cl, Br, I or OSO2R3; and
 R3 = alkyl or aryl.
 INDEPENDENT CLAIMS are also included for the following:
 (A) preparation of (IV) involving step (a);
 (B) preparation of (V) involving steps (a) and (b); and
 (C) preparation of (VII) involving steps (a)-(c).
 ACTIVITY - Antiandrogenic; cytostatic; dermatological;
 antiseborrheic; depilatory.
 MECHANISM OF ACTION - None given.
 USE - For the preparation of an N-(substituted phenyl)-3-alkyl, aryl,
 or heteroarylsulfonyl-2-hydroxy-2-alkyl or haloalkylpropanamide (e.g.
 N-(4-cyano-3-trifluoromethylphenyl)-3-(4-fluoro-phenyl)sulfonyl)-2-
 hydroxy-2-methylpropanamide) (bicalutamide) (claimed) which are
 useful in the treatment of malignant or benign prostatic disease or
 androgen dependent disease conditions such as acne, hirsutism or
 seborrhea.

ADVANTAGE - The process does not require the use of chromatographic separations and uses less expensive starting materials compared to prior art processes. (I) exhibits antiandrogenactivity.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-H; B10-A10; B10-A15; B10-D03; B14-H01B; B14-N17C; B14-R02

TECH UPTX: 20020613

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The first and second bases are selected from alkali metal hydride, alkali metal alkoxide, alkali metal amide or alkyllithium (preferably sodium hydride, potassium tert-butoxide, sodium amide or butyllithium, especially sodium hydride).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The epoxidizing agent is peracid or dioxirane (preferably peracetic acid, trifluoroperacetic acid or 3-chloroperbenzoic acid, especially trifluoroperacetic acid). The trifluoroacetic acid is formed in situ from hydrogen peroxide or trifluoroacetic anhydride. The oxidizing agent is selected from a peracid, dioxirane, hydrogen peroxide, sodium periodate, N-methylmorphine N-oxide or oxone (preferably peracid). The peracid is peracetic acid, trifluoroperacetic acid or 3-chloroperbenzoic acid (preferably trifluoroperacetic acid).

Preferred Method: Steps (a)-(d) are conducted in the presence of an aprotic solvent selected from halogenated hydrocarbon, hydrocarbon, aromatic hydrocarbon, halogenated aromatic hydrocarbon, ether, ester and/or amide. Step (a) is conducted in the presence of N,N-dimethylformamide. Step (b) is conducted in the presence of dichloromethane. Step (c) is conducted in the presence of tetrahydrofuran. Step (d) is conducted in the presence of dichloromethane.

ABEX UPTX: 20020613

EXAMPLE - To a solution of methacrylamide (153 g) in N,N-dimethyl formamide (800 ml) was added 4-cyano-3-(trifluoromethyl)phenyl fluoride (200 g) at room temperature (RT). The solution was cooled and after work up gave N-(4-cyano-3-(trifluoromethyl)phenyl)methacrylamide (A) (260 g). To a stirred solution of (A) (250 g) in dichloromethane (1.2 l) was added 30 % hydrogen peroxide (170 ml). The solution was cooled and after work up gave N-(4-cyano-3-trifluoromethyl)phenyl)methacrylamide epoxide (B) (180 g). To a 0 degrees C mixture of sodium hydride (193 g) in tetrahydrofuran (THF) (333 ml) was added a solution of 4-fluorobenzenethiol (81.8 ml) in THF (248 ml) by maintaining temperature below 25 degrees C during addition. The mixture was stirred for 5 minutes and a solution of (B) (166 g) in THF (830 ml) was added. After work up it gave N-(4-cyano-3-trifluoromethyl)phenyl)-3-((4-fluorophenyl)thio)-2-hydroxy-2-methylpropanamide (C) (244.74 g). To a solution of (C) (244.74 g) in dichloromethane (1.5 L) was added 30 % hydrogen peroxide (141.6 ml), cooled and added trifluoroacetic anhydride (520.6 ml). After work up this gave N-(4-cyano-3-trifluoromethyl)phenyl)-3-(4-fluorophenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (bicalutamide) (255.2 g; 97 % yield).

DEFINITIONS - Preferred Definitions:

R3 = trifluoromethyl;

Y' = cyano or nitro;

R = trifluoromethyl;

R1 = methyl; and

R2 = 1-4C alkyl, phenyl, p-fluorophenyl, thiazol-2-yl,

4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl or 2-pyridyl.

L92 ANSWER 8 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-355089 [37] WPIX

DNC C2001-109964

TI Asymmetric synthesis of enantiomers of acylanilides and/or their intermediates, particularly **bicalutamide**, useful e.g. for treating prostate cancer.

DC B05

IN EKWURIBE, N N; EKWURIBE, N

PA (NOBE-N) NOBEX CORP; (EKWU-I) EKWURIBE N N

CYC 95

PI WO 2001028990 A2 20010426 (200137)* EN 44 C07C315-00 <--
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TZ UG ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
 DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
 LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
 SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
 AU 2001019686 A 20010430 (200148) C07C315-00 <--
 NO 2002001831 A 20020619 (200253) C07C315-00 <--
 EP 1222165 A2 20020717 (200254) EN C07C317-34
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI
 CZ 2002001340 A3 20020814 (200263) C07C315-00 <--
 BR 2000014889 A 20021231 (200309) C07C315-00 <--
 KR 2002091047 A 20021205 (200324) C07C315-00 <--
 JP 2003512351 W 20030402 (200325) 53 C07C319-20
 HU 2002003785 A2 20030428 (200337) C07C317-34
 US 6583306 B1 20030624 (200343) C07C315-00 <--
 CN 1409702 A 20030409 (200345) C07C317-34
 ZA 2002002947 A 20030923 (200368) 66 C07C000-00
 US 2004030130 A1 20040212 (200412) C07D279-12
 NZ 518392 A 20040227 (200418) C07C315-00 <--

ADT WO 2001028990 A2 WO 2000-US41233 20001018; AU 2001019686 A AU 2001-19686
 20001018; NO 2002001831 A WO 2000-US41233 20001018, NO 2002-1831 20020418;
 EP 1222165 A2 EP 2000-982690 20001018, WO 2000-US41233 20001018; CZ
 2002001340 A3 WO 2000-US41233 20001018, CZ 2002-1340 20001018; BR
 2000014889 A BR 2000-14889 20001018, WO 2000-US41233 20001018; KR
 2002091047 A KR 2002-704966 20020418; JP 2003512351 W WO 2000-US41233
 20001018, JP 2001-531790 20001018; HU 2002003785 A2 WO 2000-US41233
 20001018, HU 2002-3785 20001018; US 6583306 B1 Provisional US 1999-160412P
 19991019, US 2000-691621 20001018; CN 1409702 A CN 2000-817022 20001018;
 ZA 2002002947 A ZA 2002-2947 20020415; US 2004030130 A1 Provisional US
 1999-160412P 19991019, Div ex US 2000-691621 20001018, US 2003-444343
 20030523; NZ 518392 A NZ 2000-518392 20001018, WO 2000-US41233 20001018

FDT AU 2001019686 A Based on WO 2001028990; EP 1222165 A2 Based on WO
 2001028990; CZ 2002001340 A3 Based on WO 2001028990; BR 2000014889 A Based
 on WO 2001028990; JP 2003512351 W Based on WO 2001028990; HU 2002003785 A2
 Based on WO 2001028990; US 2004030130 A1 Div ex US 6583306; NZ 518392 A
 Based on WO 2001028990

PRAI US 1999-160412P 19991019; US 2000-691621 20001018;
 US 2003-444343 20030523

IC ICM C07C000-00; C07C315-00; C07C317-34; C07C319-20; C07D279-12
 ICS C07C231-00; C07C255-49; C07C315-02; C07C317-14; C07C317-46;
 C07C319-14; C07C323-52; C07C323-60; C07M007-00

ICA C07B053-00; C07D317-34; C07D498-04

ICI C07M007:00

AB WO 200128990 A UPAB: 20020226
 NOVELTY - Enantiomers of acylanilides and/or their intermediates are
 prepared with improved separation, and the preferred (R)-enantiomer of
bicalutamide is prepared using (S) citramalic acid as a starting
 material.

DETAILED DESCRIPTION - Asymmetric synthesis of an enantiomer of an acylanilide, or a derivative, comprises: (a) contacting a compound having a ring structure that, when opened, provides a substituent having the structure (I), with a compound of formula R7-R6-X1-H (II) to give (III);
 R1 = 1-4C alkyl or 1-4C haloalkyl;

R2 = 1-6C alkyl;
 R3 = CH2OR4;
 R4 = H, benzyl, C(O)Me or C(O)OR5;
 R5 = H or alkyl;
 R6 = a direct link or 1-6C alkyl;
 R7 = 1-6C alkyl, 2-6C alkenyl, 1-6C hydroxyalkyl or 3-6C cycloalkyl;
 phenyl substituted with 1-3 Q; naphthyl; or Het;
 Q = H, halo, NO2, carboxy, carbamoyl or CN; or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulfonyl, alkylsulfonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulfinyl, perfluoroalkylsulfonyl, alkoxycarbonyl or N-alkylcarbamoyl, each of 1-4C; or phenyl, phenylthio, phenylsulfinyl or phenylsulfonyl;

Het = a 5-6 membered optionally unsaturated heterocyclic containing 1-3 heteroatoms (O, N or S), which may be a single ring or fused to a benzo-ring; and the heterocyclic is optionally substituted with 1 or 2 halo, CN or NH2, or alkyl, alkoxy, alkylsulfinyl or alkylsulfonyl, each of 1-4C, or oxy or OH, or 1 or 2 oxo substituents;

X1 = O, S, -SO-, -SO2-, -NH- or -NR8-;

R8 = 1-6C alkyl;

X2 = as defined for X1 or -NR8a-;

R8a = oxidized alkylimino;

and (b) treating (III) under suitable conditions to give a pure enantiomer of an acylanilide or derivative.

INDEPENDENT CLAIMS are included for the following: (1) new intermediates of formula (IV) and their preparation;

R9 = H or straight, branched or cyclic alkyl;

R10 = alkyl, aryl or R11X43;

R11 = alkyl;

X4 = alkyl, halo or aryl;

X3 = a leaving group;

and (2) preparation of optically active compounds (III); (3) preparation of a pure enantiomer of an acylanilide or derivative of formula (XIVA) from citramalic acid by the following reaction scheme:

(i) aldol condensation with citramalic acid (X) to give (XV);

(ii) decarboxylating (XV) to give (IVA);

(iii) hydrolyzing (IVA) to give (XXIII);

(iv) treating (XXIII) with (II) to give (XVIII);

(v) treating (XVIII) with (XIII);

(vi) oxidizing the product from (v) to give (XIVA).

R14 = CN, carbamoyl, NO2, F, Cl, Br or I; or alkanoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulfinyl or perfluoroalkylsulfonyl each having 1-4C; or phenylthio, phenylsulfinyl or phenylsulfonyl;

R13 = R14, H, 1-4C alkyl or 1-4C alkoxy; and

R15 = H or halo.

ACTIVITY - Anticancer.

MECHANISM OF ACTION - None given

USE - The acylanilide bicalutamide (N-(4-cyano-3-(trifluoromethyl)phenyl)-3-((4-fluorophenyl)sulfonyl)-2-hydroxy-2-methyl-propanamide) (particularly R-enantiomer) is useful for treating androgen-dependent diseases, e.g. prostate cancer.

ADVANTAGE - The asymmetric methods are more cost effective than conventional methods, and do not require use of the expensive (R) proline as in previous methods.

Dwg.0/3

FS CPI

FA AB; GI; DCN

MC CPI: B10-D03; B14-H01

TECH UPTX: 20010704

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Methods: The compound having a ring structure is of formula (IV), (VIII) or (XI), and reacts with (II) to form (V), (IX) or (XII) respectively.

X5 = a leaving group.

Compound (V), (IX) or (XII) is reacted to form (III).

In step (b), (III) is treated with a compound of formula (XIII) to form acylanilide (XIV):

Preferred Preparation of (XIVA): Step (i) is carried out with bromal in the presence of sulfuric acid. In step (ii) decarboxylation is carried out by decarboxylatively brominating with 2-mercaptopyridine N-oxide, dicyclohexylcarbodiimide and CBrCl₃. In step (iii) hydrolysis is carried out with HCl. In step (iv), (II) is 4-fluorobenzenethiol, and in step (v), (XVIII) is reacted with thionyl chloride to give the acid chloride, then reacted with 4-amino-2-trifluoromethylbenzonitrile. Oxidation in step (vi) is carried out with meta-chloroperbenzoic acid. (S) Citramalic acid produces (R)-bicalutamide, and (R)-citramalic acid produces the (S)-enantiomer.

ABEX

UPTX: 20010704

SPECIFIC COMPOUNDS - 5-Bromomethyl-5-methyl-2-tribromomethyl (1,3)dioxolan-4-one (IVa) is specifically claimed.

EXAMPLE - Bromal (89.1 mmol) and (S)-citramalic acid (74.2 mmol) were cooled to 0degreesC under an inert atmosphere, and sulfuric acid (25 ml) was added dropwise with stirring. After 2 hours, cooling was removed and the mixture was stirred overnight at room temperature. The solution was diluted with ice and extracted repeatedly with ethyl acetate. The organic layer was back extracted with water, dried and filtered. The filtrate was concentrated, and **crystallization** from toluene/hexanes gave 4 methyl-5-oxo-2-tribromomethyl-(1,3,1-dioxolan-4-yl)-acetic acid (60% yield).

This compound and 2-mercaptopyridine N-oxide were suspended in CBrCl₃, and refluxed. A solution of dicyclohexylcarbodiimide in CBrCl₃ was added slowly over 30 minutes. After stirring for 1 hour, the product was purified by silica gel chromatography to give (IVa) (65% yield), m.pt. 110-113degreesC.

(IVa) was dissolved in a mixture of isopropanol:1M NaOH (1:1). After 3 hours, 4-fluorobenzenethiol was added, and the mixture was stirred overnight. pH was adjusted to 8 and the mixture was extracted with CH₂Cl₂. Work up and **recrystallization** from CHCl₃/petroleum ether gave 3-(4-fluoro phenylsulfanyl)-2-hydroxy-2-methyl-propionic acid. (80% yield), m.pt. 73-75degreesC.

The hydroxyacid (8.5 mmol) and 4-amino-2 trifluoromethylbenzonitrile (11 mmol) were dissolved in dry dimethylacetamide (15 ml) under an inert atmosphere. The solution was cooled to -10degreesC, and thionyl chloride (10 mmol) was added slowly. The mixture was stirred for 15 minutes at -10degreesC, and overnight at room temperature, then diluted with CH₂Cl₂ and extracted with saturated NaHCO₃. Work up and purification by silica gel chromatography gave N-(4-cyano-3-trifluoromethyl phenyl)-3-(4-fluoro-phenylsulfanyl)-2-hydroxy-2-methyl propionamide (45%).

This compound (3.19 mmol) was dissolved in CH₂Cl₂ (43 ml) and meta-chloroperbenzoic acid (9.57 mmol) was added. After stirring overnight at room temperature, the mixture was diluted with ethyl acetate and extracted with Na₂SO₃ and NaHCO₃. Work up and purification by silica gel chromatography gave **bicalutamide** (94% yield), m.pt. 178degreesC.

L92 ANSWER 9 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-343585 [36] WPIX

DNC C2001-106402

TI Resolution of intermediates useful in synthesis of acylanilide compounds, e.g., the anticancer agent **bicalutamide**, especially by resolving a cinchonidine salt by **crystallization**.

DC B05

IN EKWURIBE, N N; JAMES, K D; RAJAGOPALAN, J

PA (NOBE-N) NOBEX CORP

CYC 95

PI WO 2001034563 A1 20010517 (200136)* EN 27 C07C315-06 <--

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
 DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
 LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
 SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001026195 A 20010606 (200152) C07C315-06 <--
 BR 2000015124 A 20020702 (200252) C07C315-06 <--
 NO 2002001999 A 20020620 (200253) C07C000-00
 EP 1224167 A1 20020724 (200256) EN C07C315-06 <--
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI

CZ 2002001434 A3 20021113 (200282) C07C315-06 <--
 KR 2002067509 A 20020822 (200310) C07C315-06 <--
 HU 2002003186 A2 20030128 (200323) C07C315-06 <--
 JP 2003513955 W 20030415 (200328) 30 C07B057-00
 CN 1413188 A 20030423 (200347) C07C315-06 <--
 US 6593492 B1 20030715 (200348) C07C067-02
 ZA 2002003228 A 20030923 (200368) 45 C07C000-00
 MX 2002004225 A1 20021001 (200370) C07C315-06 <--
 NZ 518552 A 20031031 (200380) C07C315-06 <--

ADT WO 2001034563 A1 WO 2000-US41609 20001025; AU 2001026195 A AU 2001-26195
 20001025; BR 2000015124 A BR 2000-15124 20001025, WO 2000-US41609
 20001025; NO 2002001999 A WO 2000-US41609 20001025, NO 2002-1999 20020426;
 EP 1224167 A1 EP 2000-989719 20001025, WO 2000-US41609 20001025; CZ
 2002001434 A3 WO 2000-US41609 20001025, CZ 2002-1434 20001025; KR
 2002067509 A KR 2002-705357 20020426; HU 2002003186 A2 WO 2000-US41609
 20001025, HU 2002-3186 20001025; JP 2003513955 W WO 2000-US41609 20001025,
 JP 2001-536512 20001025; CN 1413188 A CN 2000-817760 20001025; US 6593492
 B1 Provisional US 1999-161884P 19991027, US 2000-695884 20001025; ZA
 2002003228 A ZA 2002-3228 20020423; MX 2002004225 A1 WO 2000-US41609
 20001025, MX 2002-4225 20020426; NZ 518552 A NZ 2000-518552 20001025, WO
 2000-US41609 20001025

FDT AU 2001026195 A Based on WO 2001034563; BR 2000015124 A Based on WO
 2001034563; EP 1224167 A1 Based on WO 2001034563; CZ 2002001434 A3 Based
 on WO 2001034563; HU 2002003186 A2 Based on WO 2001034563; JP 2003513955 W
 Based on WO 2001034563; MX 2002004225 A1 Based on WO 2001034563; NZ 518552
 A Based on WO 2001034563

PRAI US 1999-161884P 19991027; US 2000-695884 20001025

IC ICM C07B057-00; C07C000-00; C07C067-02; C07C315-06

ICS C07C315-04; C07C317-28; C07C317-46

AB WO 200134563 A UPAB: 20010628

NOVELTY - A pure enantiomer of an acylanilide is prepared by:

(a) resolving an intermediate (I); and

(b) treating the resolved intermediate (I) under conditions
 sufficient to give a pure enantiomer of an acylanilide.

DETAILED DESCRIPTION - Preparation of a pure enantiomer of an
 acylanilide comprises:

(a) resolving an intermediate compound of formula (I); and

(b) treating the resolved intermediate (I) under conditions
 sufficient to give a pure enantiomer of an acylanilide.

R1 = T' or 1-4C haloalkyl;

R2 = 1-6C alkylene;

R3 = 1-6C alkylene, or a bond;

R4 = 1-6C alkyl, 2-6C alkenyl, 1-6C hydroxyalkyl or 3-6C cycloalkyl;

Ph (optionally substituted by 1-3 halo, NO₂, carboxy, carbamoyl, CN, T',
 T'O, 1-4C alkanoyl, T'S, T'SO, T'SO₂, Q, QS, QSO, QSO₂, T'OOC, CONHT', Ph,
 PhS, PhSO or PhSO₂); naphthyl; or Het (optionally substituted by 1-2 halo,
 CN, amino, T', T'S, T'SO, T'SO₂, oxy or hydroxy substituents, or (if
 sufficiently saturated) 1-2 oxo substituents);

X1 = O, S, SO, SO₂, NH or NR₅;

R5 = 1-6C alkyl;

T', Q = 1-4C alkyl and 1-4C perfluoroalkyl respectively;

Ph = phenyl; and

Het = a 5-6 membered saturated or unsaturated heterocycle which

contains 1-3 O, N and/or S atoms and which is optionally fused to a benzo ring.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - None given.

USE - The process is useful for production of pure enantiomers of acylanilide compounds, especially **bicalutamide**, which is useful in treatment of prostate cancer.

ADVANTAGE - The process allows resolution of enantiomers of intermediate compounds before reaction with expensive materials which introduce other portions to the final molecule. This means that these expensive materials are not used in production of inactive enantiomers which will be discarded. The process thus allows more cost effective production of materials such as **bicalutamide**.

Dwg.0/3

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-H; B10-A10; B10-A15; B10-D03; B14-H01B

TECH UPTX: 20010628

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred process: the resolution step comprises resolving the intermediate compound of formula (I) by **crystallization** or high performance liquid chromatography. Resolution by **crystallization** comprises contacting (I) with a chiral base to give a diastereomeric mixture of a chiral salt, resolving the mixture by **crystallization** and recovering a pure enantiomer of (I). The chiral base is especially (-)-cinchonidine. The solvent system used for resolution by **crystallization** is especially a mixture of methylene chloride and diethyl ether, most especially a mixture of 1-40 volume % of methylene chloride and 60-99 vol. % of diethyl ether. For production of **bicalutamide**, an intermediate compound (I; R1 = Me, R2 = CH2, R3 = a bond, R4 = 4-fluorophenyl and X1 = SO2) is resolved as outlined above, then the resolved compound can be reacted with a compound of formula (II) to give a pure enantiomer of **bicalutamide**.

R7 = perfluoroalkyl.

ABEX UPTX: 20010628

EXAMPLE - In a typical process, the salt of an (R,S)-hydroxyacid and (-)-cinchonidine was formed by mixing a solution of the hydroxyacid (1 equivalent) with a solution of (-)-cinchonidine (1 equivalent). The cinchonidine was typically dissolved in chloroform while the acid was dissolved in, e.g., chloroform, methylene chloride, ethyl acetate or ethanol. The mixture was then stirred at room temperature overnight. The solvent was then removed by rotary evaporation. The salt (typically 20 mg) was then placed in a vial and treated with ethyl ether (2 ml). Methylene chloride was then added, with shaking, until all of the salt had been solubilized. The solution was then placed at 4 degrees C for **crystallization**. After **crystallization**, the supernatant was removed. The **crystals** were then dissolved in deuterated chloroform. The ratio of (R)- to (S)-enantiomer could then be assayed by integration of the fluorine signal using ¹⁹F NMR.

L92 ANSWER 10 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-102880 [11] WPIX

DNC C2001-030165

TI Synthesis of **bicalutamide**, a selective anti-androgen, involves the oxidation of its thioether precursor.

DC B05

IN BOR, A; BRLIK, J; DEMETER, A; GALIK, G; HORVATH, J; SOEROES, B; TRISCHLER, F; TUBA, Z

PA (RICT) RICHTER GEDEON VEGYESZETI GYAR

CYC 94

PI WO 2001000608 A1 20010104 (200111)* EN 33 C07D327-10

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ
 EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
 LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
 SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000052397 A 20010131 (200124)

HU 9901937 A1 20010428 (200131) C07C317-32

EP 1189898 A1 20020327 (200229) EN C07D327-10

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI

EP 1189898 B1 20030312 (200319) EN C07D327-10

R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

DE 60001657 E 20030417 (200333) C07D327-10

ES 2188550 T3 20030701 (200347) C07D327-10

ADT WO 2001000608 A1 WO 2000-HU49 20000526; AU 2000052397 A AU 2000-52397
 20000526; HU 9901937 A1 HU 1999-1937 19990610; EP 1189898 A1 EP
 2000-937111 20000526, WO 2000-HU49 20000526; EP 1189898 B1 EP 2000-937111
 20000526, WO 2000-HU49 20000526; DE 60001657 E DE 2000-00001657 20000526,
 EP 2000-937111 20000526, WO 2000-HU49 20000526; ES 2188550 T3 EP
 2000-937111 20000526

FDT AU 2000052397 A Based on WO 2001000608; EP 1189898 A1 Based on WO
 2001000608; EP 1189898 B1 Based on WO 2001000608; DE 60001657 E Based on
 EP 1189898, Based on WO 2001000608; ES 2188550 T3 Based on EP 1189898

PRAI HU 1999-1937 19990610

IC ICM C07C317-32; C07D327-10

ICS C07C253-30; C07C303-28; C07C309-66; C07C315-02; C07C317-46;
 C07C319-14; C07C323-60

AB WO 2001000608 A UPAB: 20010224

NOVELTY - A multistep process for making optically pure enantiomers of
bicalutamide (I) involving the oxidation of the precursor
 thioether (II) is new.

DETAILED DESCRIPTION - A process for making racemic or optically pure
 R(-) or S(+) **bicalutamide** (I) comprises:

(1) reacting racemic or optically pure 2,3-dihydroxy-2-methyl-
 propionic acid (VII) with thionyl chloride in a halohydrocarbon or in an
 aromatic solvent with an aromatic amine base;

(2) reacting the resulting 4-chloro-carbonyl-4-methyl-1,3,2-
 dioxathiolane-2-one (VI) with 4-cyano-3 trifluoromethylaniline in an inert
 solvent with a tertiary amine at between 0 and -40 deg. C;

(3) hydrolyzing the resulting 4-((4-cyano-3-(trifluoromethyl)-
 anilino)-carbonyl)-4-methyl-1,3,2-dioxathiolanone-2-one (V) under aqueous
 basic conditions;

(4) sulfonating the N-(4-cyano-3-(trifluoromethyl)-phenyl)-2,3-
 dihydroxy-2-methyl-propionamide (IV) with a sulfonyl halogenide RSO₂X in
 a halohydrocarbon solvent in the presence of a tertiary amine base;

(5) reacting the resulting sulfonic ester (III) with 4-fluorophenol
 in the presence of a base; and

(6) oxidizing the thioether (II) with

(a) an inorganic peroxy salt in a solvent/water mixture optionally
 (for solvents immiscible in water) in the presence of a transfer catalyst,
 or

(b) aqueous hydrogen peroxide

(1) in a 1-4C aliphatic carboxylic acid,

(2) under aqueous basic conditions with a water-miscible organic
 solvent, or

(3) in an water-immiscible organic solvent in the presence of a phase
 transfer catalyst and a vanadium or chromium salt.

R = methyl, p-tolyl or p-bromophenyl; and

X = halo.

ACTIVITY - Anti-androgen.

USE - Useful for making **bicalutamide** with selective
 anti-androgen activity.

ADVANTAGE - The starting material, available cheaply, allows the
 production of pure enantiomers. Oxidative steps are safe and do not cause

environmental pollution. The use of inflammable sodium hydride is avoided. The use of harmful reagents such as potassium cyanide in acidic medium are avoided. No special equipment is needed for commercial manufacture e.g. acid-resistant autoclaves. Product is pure enough to only require simple purification methods to make the final product. Existing processes require the separation of the optically pure enantiomers from a racemic mix leading to high levels of wastage. Whereas the new method allows more of the starting materials to be converted into final optically pure enantiomer with less waste.

Dwg.0/6

FS CPI

FA AB; DCN

MC CPI: B05-A01A; B05-A01B; B05-A03B; B07-C; B07-D04C; B10-A04; B10-A09C; B10-A10; B10-A15; B10-A22; B10-B04A; B10-B04B; B10-C04D; B10-C04E; B10-E02; B10-E04D; B10-H02F; B10-J02; B11-C01; B14-D02A

TECH UPTX: 20010224

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Synthesis:

(1) Halohydrocarbon is selected from dichloromethane, chloroform or 1,2-dichloroethane. The aromatic solvent is benzene, toluene or xylene. The aromatic base is pyridine.

(2) The tertiary amine base is triethylamine. The inert solvent is halohydrocarbon, aromatic hydrocarbon or an ether. The reaction is carried out between 0degreesC and -15degreesC.

(3) Aqueous alkali metal hydroxide makes aqueous basic conditions.

(4) The halohydrocarbon solvent is dichloromethane and the tertiary amine base is pyridine.

(5) The base is sodium hydroxide in isopropanol.

(6) The inorganic peroxy salt is a mixture of 2KHSO5KHSO4 K2SO4 (Oxone). The solvent mix is methanol and water, dichloromethane or ethyl acetate and water with a phase transfer catalyst. The preferred carboxylic acids are formic and acetic acid. Optionally (II) is oxidized in a basic medium of aqueous alkali metal carbonate solution with acetonitrile and/or 1-4C alkanol (preferably methanol) as a water-miscible solvent with hydrogen peroxide; or in dichloromethane with water in the presence of a quaternary ammonium salt as a phase transfer catalyst with sodium tungstate and aqueous hydrogen peroxide. The phase transfer catalyst is tetrabutylammonium hydrogensulfate, cetylammmonium chloride or tetrabutylammmonium chloride.

ABEX UPTX: 20010224

SPECIFIC COMPOUNDS - The use of Oxone as an inorganic peroxy salt, tetrabutylammonium hydrogensulfate and 2 other phase transfer catalysts are specifically claimed.

EXAMPLE - A mix of (VII) (75g) in toluene (2 Liters) and pyridine (1.5ml) was cooled to 10degreesC before adding thionyl chloride (1.524mol) and refluxing for 4 hours before concentrating under reduced pressure and distilling in vacuum to make (VI). A solution of 4-cyano-3-trifluoromethylaniline (44g) in dichloromethane (880ml) was mixed with triethylamine (90ml) before cooling to -15degreesC and adding (VI) (64ml) dropwise. The reaction was stirred at 0degreesC for 3 hours before extraction with 10% hydrochloric acid (500ml), drying the organic layer over sodium sulfate and concentrating under reduced pressure. The residue (V) was dissolved in tetrahydrofuran (1L) and 10% sodium hydroxide (440ml) at 10degreesC. After mixing for 0.5 hours the pH was titrated to 2 with concentrated hydrochloric acid the solution was evaporated to 100ml and the residue was dissolved in ethyl acetate (to make 260ml), treated with charcoal, and filtered before adding petroleum ether (520ml). The precipitated **crystals** (IV) were filtered and dried at 60degreesC in a vacuum. A solution of (IV) (5g) in dry pyridine (50ml) at 0C was mixed with 4-bromo-benzene sulfonyl chloride (8.86g) for 5 hours before diluting with dichloromethane (200ml), washing 3 times in saturated aqueous sodium bicarbonate (50ml), twice with 10% aqueous hydrochloric acid (50ml) and in brine (50ml). The organic layer was dried over sodium sulfate, concentrated under vacuum, and the residue was

crystallized in 1 part ethylacetate/ 5 parts petroleum ether to give (III). 4-Fluorothiophenol (25.6g) in isopropanol (500ml) was mixed with sodium hydroxide (8.4g) in water (400ml) under nitrogen for 2 hours before adding (III) (58.6g) in isopropanol (500ml) and mixing for another 5 hours. The mix was titrated to pH7 with concentrated hydrochloric acid before treatment with charcoal at reflux temperature. After evaporating most of the isopropanol under vacuum, 2% aqueous sodium hydroxide (250ml) was added and stirred before filtering and washing of the settled **crystals**. The dried **crystals** (II) were **recrystallized** as above. A solution of (II) (52g) in acetic acid (520ml) at 10degreesC was mixed with 30% aqueous hydrogen peroxide (156ml) overnight before adding saturated aqueous sodium bicarbonate (3L) and extracting 3 times with dichloromethane (500ml). The combined organic layers were washed with brine (500ml) before drying over sodium sulfate and concentrating under reduced pressure. The residue was dissolved in ethyl acetate (500ml), cooled to 5degreesC and was mixed with petroleum ether (2L). The precipitated **crystals** were filtered, washed with petroleum ether (40ml), cooled to 0degreesC and dried at 60degreesC in a vacuum to make **bicalutamide** (47.25g: yield 84.15%).

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